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WO 02/48113 A1

(54) Title: CYCLIZATION PROCESS STEP IN THE MAKING OF QUINOLONES AND NAPHTHYRIDINES

(57) Abstract: Process for making a compound having a structure according to Formula (I), the process comprising reacting an organosilicon reagent with a compound having a structure according to Formula (A).

CYCLIZATION PROCESS STEP IN THE MAKING OF QUINOLONES AND NAPHTHYRIDINES

FIELD OF THE INVENTION

The subject invention relates to processes for making quinolones and quinolone derivatives; which are compounds that are active antibacterial and/or are anti-HIV agents. The invention also relates to useful intermediates in making these compounds.

BACKGROUND OF THE INVENTION

The chemical and medical literature describes compounds that are said to be antimicrobial, i.e., capable of destroying or suppressing the growth or reproduction of microorganisms, such as bacteria. For example, such antibacterials and other antimicrobials are described in Antibiotics, Chemotherapeutics, and Antibacterial Agents for Disease Control (M. Grayson, editor, 1982), and E. Gale et al., The Molecular Basis of Antibiotic Action 2d edition (1981).

The mechanism of action of these antibacterials vary. However, they are generally believed to function in one or more of the following ways: by inhibiting cell wall synthesis or repair; by altering cell wall permeability; by inhibiting protein synthesis; or by inhibiting synthesis of nucleic acids. For example, beta-lactam antibacterials act through inhibiting the essential penicillin binding proteins (PBPs) in bacteria, which are responsible for cell wall synthesis. As another example, quinolones act, at least in part, by inhibiting synthesis of DNA, thus preventing the cell from replicating.

The pharmacological characteristics of antimicrobials, and their suitability for any given clinical use, vary. For example, the classes of antimicrobials (and members within a class) may vary in 1) their relative efficacy against different types of microorganisms, 2) their susceptibility to development of microbial resistance and 3) their pharmacological characteristics, such as their bioavailability, and biodistribution. Accordingly, selection of an appropriate antibacterial (or other antimicrobial) in a given clinical situation requires analysis of many factors, including the type of organism involved, the desired method of administration, the location of the infection to be treated and other considerations.

Cyclization processes for making intermediate compounds useful in the synthesis of quinolone, naphthyridine, and related compounds are disclosed in a number of references including the following: European Patent Application No. 0 168,733 published January 22, 1986; and U.S. Patent No. 5,703,231 issued December 30, 1997. While the methods disclosed in the those publications represent useful advances in quinolone chemistry, Applicants have

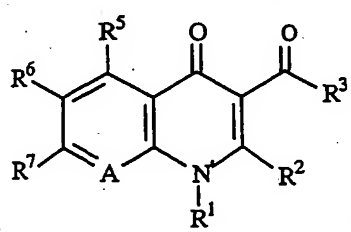
discovered that the use of certain leaving groups, not contemplated in those or other prior art references, in combination with the use of a silylating reactant provide several advantages relative to the processes disclosed in the prior art. For example, the present process allows the synthesis of various quinolones and related compounds by an intramolecular cyclization process in which the key leaving group on the starting aromatic ring precursor (depicted as XR^9 in Formula (A) below) is electron donating in nature. The aromatic ring precursor may contain other substituents which may be electron donating or electron withdrawing in nature. Certain prior cyclization methods to form quinolones disclose an electron withdrawing group as the leaving group on the starting aromatic ring and also may require the presence of other electron withdrawing groups at the ortho or para positions on that ring. See, e.g., U.S. Patent No. 5,703,231. Further, when other prior art has discussed the use of methoxy and thiomethyl leaving groups, reaction conditions disclosed are harsh insofar as they use sodium hydride and require high temperatures (140-160°C) in polar solvents.

The present process, in contrast, allows the use of a broader group of starting materials in the manufacture of quinolones, possibly leading to a more efficient and cost effective process. The process also allows the use of less harsh reaction conditions than the methods described in the art generally, which may also provide improved synthetic yields.

Accordingly, the present invention provides an improved means to obtain quinolones and derivatives of quinolones, which themselves may be active or may be intermediates for forming other active molecules.

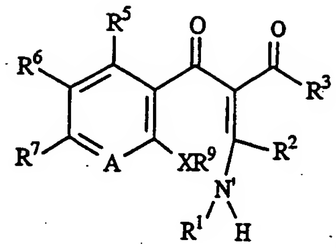
SUMMARY OF THE INVENTION

The subject invention relates to a process for making a compound having a structure according to Formula (I), or an optical isomer, diastereomer or enantiomer thereof, or a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof:



(I)

the process comprising reacting one or more organosilicon reagents with a compound having a structure according to Formula (A):



(A)

wherein with regard to Formula (I) and Formula (A):

(A) (1) A is N or C-R^8, where R^8 is selected from hydrogen, alkyl, aryl, halo, a heterocyclic ring, amino, alkylamino, arylamino, alkoxy, nitro, cyano, aryloxy, esters of hydroxy, alkylthio, arylthio, aryloxy, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and aryl esters and amides of carboxy;

(2) R^7 is selected from hydrogen, alkyl, aryl, a heterocyclic ring, amino, alkylamino, arylamino, halo, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and alkyl and aryl esters and amides of carboxy;

(3) R^6 is selected from hydrogen, halo, alkyl, aryl, a heterocyclic ring, amino, alkylamino, arylamino, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and alkyl and aryl esters and amides of carboxy;

(4) R^5 is selected from hydrogen, alkyl, aryl, cyano, a heterocyclic ring, amino, alkylamino, arylamino, alkylacyl, arylacyl, and aryl esters and amides of carboxy;

(5) R^1 is selected from a carbocyclic ring, a heterocyclic ring, lower alkyl, lower alkene, lower alkyne and -CH(R^{10})(R^{11}) where R^{10} is selected from lower alkyl and phenyl and R^{11} is -CH_2Y(O=)CR^{12} where R^{12} is selected from lower alkyl and phenyl and Y is selected from -NH-, -O- and -S-;

(6) R^2 is selected from hydrogen, alkyl, aryl, a heterocyclic ring, alkylthio and arylthio; and

(7) R^3 is selected from hydrogen, alkoxy, aryloxy, alkyl and aryl; or

(B) R^1 and R^2 can join to form a 5- or 6-membered carbocyclic or heterocyclic ring, where A, R^3, R^5, R^6, R^7 and R^8, if present, are as described in (A); or

(C) R^6 and R^7 can join to form a 5- or 6-membered carbocyclic or heterocyclic ring, where A, R^1, R^2, R^3, R^5 and R^8, if present, are as described in (A);

and wherein with regard to Formula (A):

(D) X is selected from -O- and -S- and R^9 is selected from C_1-C_{10} alkyl, aryl and heteroaryl.

The compounds of Formula (I) may themselves be effective antimicrobial or anti-HIV agents, or they may be further reacted using well known chemistry to provide a molecule having antimicrobial or anti-HIV activity. As such, the compounds of Formula (I) may be useful intermediates in the formation of other active quinolones and quinolone derivatives.

The invention also relates to novel intermediates, having a structure of Formula (A), that are useful in the present process.

DETAILED DESCRIPTION OF THE INVENTION

I. Terms and Definitions:

The following is a list of definitions for terms used herein:

"Acyl" or "carbonyl" is a radical formed by removal of the hydroxy from a carboxylic acid (i.e., R-C(=O)-). "Alkylacyl" is -C(=O)-alkyl and "Arylacyl is -C(=O)-aryl. Preferred acyl groups include (for example) acetyl, formyl, and propionyl.

"Alkyl" is a saturated hydrocarbon chain having 1 to 15 carbon atoms, preferably 1 to 10, more preferably 1 to 4 carbon atoms. "Alkene" is a hydrocarbon chain having at least one (preferably only one) carbon-carbon double bond and having 2 to 15 carbon atoms, preferably 2 to 10, more preferably 2 to 4 carbon atoms. "Alkyne" is a hydrocarbon chain having at least one (preferably only one) carbon-carbon triple bond and having 2 to 15 carbon atoms, preferably 2 to 10, more preferably 2 to 4 carbon atoms. Alkyl, alkene and alkyne chains (referred to collectively as "hydrocarbon chains") may be straight or branched and may be unsubstituted or substituted. Preferred branched alkyl, alkene and alkyne chains have one or two branches, preferably one branch. Preferred chains are alkyl. Alkyl, alkene and alkyne hydrocarbon chains each may be unsubstituted or substituted with from 1 to 4 substituents; when substituted, preferred chains are mono-, di-, or tri-substituted. Alkyl, alkene and alkyne hydrocarbon chains each may be substituted with halo, hydroxy, aryloxy (*e.g.*, phenoxy), heteroaryloxy, acyloxy (e.g., acetoxy), carboxy, aryl (*e.g.*, phenyl), heteroaryl, cycloalkyl, heterocycloalkyl, spirocycle, amino, amido, acylamino, keto, thioketo, cyano, or any combination thereof. Preferred hydrocarbon groups include methyl, ethyl, propyl, isopropyl, butyl, vinyl, allyl, butenyl, and exomethylenyl.

"Alkoxy" is an oxygen radical having a hydrocarbon chain substituent, where the hydrocarbon chain is an alkyl or alkenyl (i.e., -O-alkyl or -O-alkenyl) that is unsubstituted or substituted as described above. In the case of substituted alkoxy, preferred substituents include

1-5 fluorine atoms. Preferred alkoxy groups include (for example) methoxy, di-fluoro methoxy, ethoxy, penta-fluoro ethoxy, propoxy and allyloxy.

Also, as referred to herein, a "lower" alkoxy, alkyl, alkene or alkyne moiety (e.g., "lower alkyl") is a chain comprised of 1 to 6, preferably from 1 to 4, carbon atoms in the case of alkyl and alkoxy, and 2 to 6, preferably 2 to 4, carbon atoms in the case of alkene and alkyne.

"Alkylphosphonyl" is -PO_3-alkyl (e.g. -PO_3-CH_3).

"Alkylsulfonyl" is -SO_2-alkyl (e.g., -SO_2-CH_3).

"Alkylthio" is -S-alkyl (e.g. -S-CH_3).

"Amino" refers to -NH_2. "Alkylamino" is an amino substituted with at least one alkyl moiety (e.g., -$NH(CH_3)$). "Arylamino" is an amino substituted with at least one aryl moiety (e.g., -$NH(C_6H_5)$).

"Aryl" is an aromatic hydrocarbon ring. Aryl rings are monocyclic or fused bicyclic ring systems. Monocyclic aryl rings contain 6 carbon atoms in the ring. Monocyclic aryl rings are also referred to as phenyl rings. Bicyclic aryl rings contain from 8 to 17 carbon atoms, preferably 9 to 12 carbon atoms, in the ring. Bicyclic aryl rings include ring systems wherein one ring is aryl and the other ring is aryl, cycloalkyl, or heterocycloakyl. Preferred bicyclic aryl rings comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Aryl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Aryl may be substituted with halo, cyano, nitro, hydroxy, carboxy, amino, acylamino, alkyl, heteroalkyl, haloalkyl, phenyl, aryloxy, alkoxy, heteroalkyloxy, carbamyl, haloalkyl, methylenedioxy, heteroaryloxy, or any combination thereof. Preferred aryl rings include naphthyl, tolyl, xylyl, and phenyl. The most preferred aryl ring radical is phenyl.

"Aryloxy" is an oxygen radical having an aryl substituent (i.e., -O-aryl). Preferred aryloxy groups include (for example) phenoxy, napthyloxy, methoxyphenoxy, and methylenedioxyphenoxy.

"Arylphosphonyl" is -PO_3-aryl (e.g., - PO_3-C_6H_5).

"Arylsulfonyl" is -SO_2-aryl (e.g., -SO_2-C_6H_5).

"Arylthio" is -S-aryl (e.g., -S-C_6H_5).

"Biohydrolyzable amides" are aminoacyl, acylamino, or other amides of the compounds of the invention, where the amide does not essentially interfere, preferably does not interfere, with the activity of the compound, or where the amide is readily converted <u>in vivo</u> by a host to yield an active compound.

"Biohydrolyzable imides" are imides of compounds of the invention, where the imide does not essentially interfere, preferably does not interfere, with the activity of the compound, or where the imide is readily converted in vivo by a host to yield an active compound. Preferred imides are hydroxyimides.

"Biohydrolyzable esters" are esters of compounds of the invention, where the ester does not essentially interfere, preferably does not interfere, with the antimicrobial activity of the compound, or where the ester is readily converted in a host to yield an active compound. Many such esters are known in the art, as described in U.S. Patent No. 4,783,443, issued to Johnston and Mobashery on November 8, 1988 (incorporated by reference herein). Such esters include lower alkyl esters, lower acyloxy-alkyl esters (such as acetoxymethyl, acetoxyethyl, aminocarbonyloxymethyl, pivaloyloxymethyl and pivaloyloxyethyl esters), lactonyl esters (such as phthalidyl and thiophthalidyl esters), lower alkoxyacyloxyalkyl esters (such as methoxycarbonyloxymethyl, ethoxycarbonyloxyethyl and isopropoxycarbonyloxyethyl esters), alkoxyalkyl esters, choline esters and alkylacylaminoalkyl esters (such as acetamidomethyl esters).

"Carbocyclic ring" encompasses both cycloalkyl and aryl moieties, as those terms are defined herein.

"Carbonyl" is -C(=O)-.

"Cycloalkyl" is a saturated or unsaturated hydrocarbon ring. Cycloalkyl rings are not aromatic. Cycloalkyl rings are monocyclic, or are fused, spiro, or bridged bicyclic ring systems. Monocyclic cycloalkyl rings contain from about 3 to about 9 carbon atoms, preferably from 3 to 7 carbon atoms, in the ring. Bicyclic cycloalkyl rings contain from 7 to 17 carbon atoms, preferably from 7 to 12 carbon atoms, in the ring. Preferred bicyclic cycloalkyl rings comprise 4-, 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Cycloalkyl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Cycloalkyl may be substituted with halo, cyano, alkyl, heteroalkyl, haloalkyl, phenyl, keto, hydroxy, carboxy, amino, acylamino, aryloxy, heteroaryloxy, or any combination thereof. Preferred cycloalkyl rings include cyclopropyl, cyclopentyl, and cyclohexyl.

"Halo" or "halogen" is fluoro, chloro, bromo or iodo. Preferred halo are fluoro, chloro and bromo; more preferred typically are chloro and fluoro, especially fluoro.

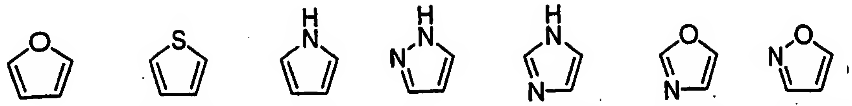
"Haloalkyl" is a straight, branched, or cyclic hydrocarbon substituted with one or more halo substituents. Preferred are C_1-C_{12} haloalkyls; more preferred are C_1-C_6 haloalkyls; still

more preferred still are C_1-C_3 haloalkyls. Preferred halo substituents are fluoro and chloro. The most preferred haloalkyl is trifluoromethyl.

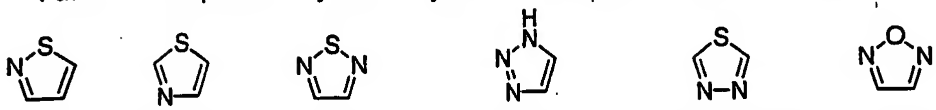
"Heteroatom" is a nitrogen, sulfur, or oxygen atom. Groups containing more than one heteroatom may contain different heteroatoms.

"Heteroalkyl" is a saturated or unsaturated chain containing carbon and at least one heteroatom, wherein no two heteroatoms are adjacent. Heteroalkyl chains contain from 2 to 15 member atoms (carbon and heteroatoms) in the chain, preferably 2 to 10, more preferably 2 to 5. For example, alkoxy (i.e., -O-alkyl or -O-heteroalkyl) radicals are included in heteroalkyl. Heteroalkyl chains may be straight or branched. Preferred branched heteroalkyl have one or two branches, preferably one branch. Preferred heteroalkyl are saturated. Unsaturated heteroalkyl have one or more carbon-carbon double bonds and/or one or more carbon-carbon triple bonds. Preferred unsaturated heteroalkyls have one or two double bonds or one triple bond, more preferably one double bond. Heteroalkyl chains may be unsubstituted or substituted with from 1 to 4 substituents. Preferred substituted heteroalkyl are mono-, di-, or tri-substituted. Heteroalkyl may be substituted with lower alkyl, haloalkyl, halo, hydroxy, aryloxy, heteroaryloxy, acyloxy, carboxy, monocyclic aryl, heteroaryl, cycloalkyl, heterocycloalkyl, spirocycle, amino, acylamino, amido, keto, thioketo, cyano, or any combination thereof.

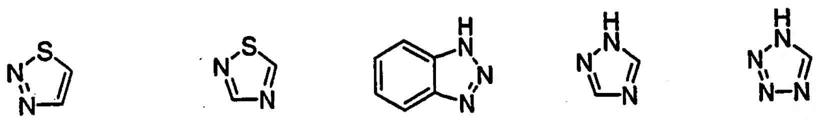
"Heteroaryl" is an aromatic ring containing carbon atoms and from 1 to about 6 heteroatoms in the ring. Heteroaryl rings are monocyclic or fused bicyclic ring systems. Monocyclic heteroaryl rings contain from about 5 to about 9 member atoms (carbon and heteroatoms), preferably 5 or 6 member atoms, in the ring. Bicyclic heteroaryl rings contain from 8 to 17 member atoms, preferably 8 to 12 member atoms, in the ring. Bicyclic heteroaryl rings include ring systems wherein one ring is heteroaryl and the other ring is aryl, heteroaryl, cycloalkyl, or heterocycloalkyl. Preferred bicyclic heteroaryl ring systems comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Heteroaryl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Heteroaryl may be substituted with halo, cyano, nitro, hydroxy, carboxy, amino, acylamino, alkyl, heteroalkyl, haloalkyl, phenyl, alkoxy, aryloxy, heteroaryloxy, or any combination thereof. Preferred heteroaryl rings include, but are not limited to, the following:



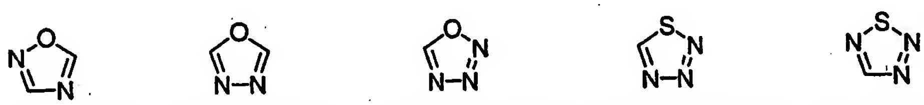
Furan Thiophene Pyrrole Pyrazole Imidazole Oxazole Isoxazole



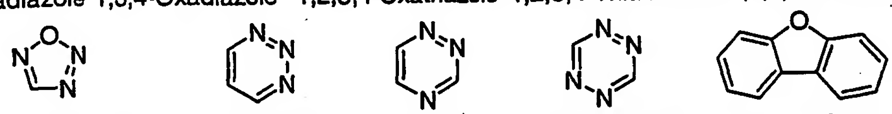
Isothiazole Thiazole 1,2,5-Thiadiazole 1,2,3-Triazole 1,3,4-Thiadiazole Furazan



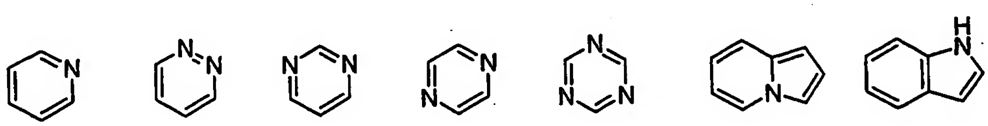
1,2,3-Thiadiazole 1,2,4-Thiadiazole Benzotriazole 1,2,4-Triazole Tetrazole



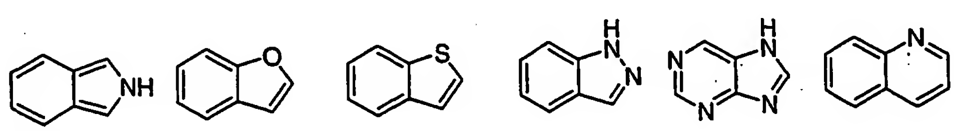
1,2,4-Oxadiazole 1,3,4-Oxadiazole 1,2,3,4-Oxatriazole 1,2,3,4-Thiatriazole 1,2,3,5-Thiatriazole



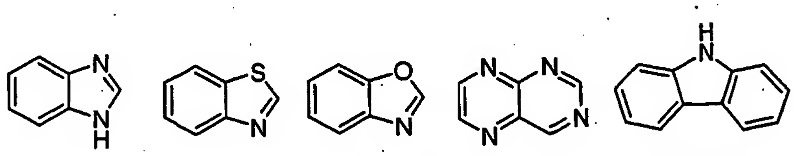
1,2,3,5-Oxatriazole 1,2,3-Triazine 1,2,4-Triazine 1,2,4,5-Tetrazine Dibenzofuran



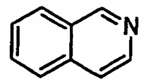
Pyridine Pyridazine Pyrimidine Pyrazine 1,3,5-Triazine Indolizine Indole

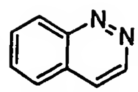


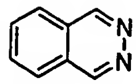
Isoindole Benzofuran Benzothiophene 1H-Indazole Purine Quinoline

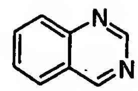


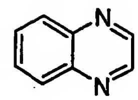
Benzimidazole Benzthiazole Benzoxazole Pteridine Carbazole

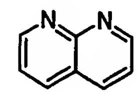

Isoquinoline

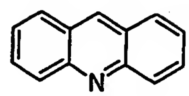

Cinnoline

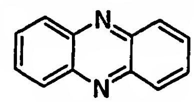

Phthalazine


Quinazoline


Quinoxaline


1,8-Napthypyridine


Acridine

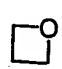

Phenazine

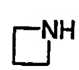
"Heteroaryloxy" is an oxygen radical having a heteroaryl substituent (i.e., -O-heteroaryl). Preferred heteroaryloxy groups include (for example) pyridyloxy, furanyloxy, (thiophene)oxy, (oxazole)oxy, (thiazole)oxy, (isoxazole)oxy, pyrmidinyloxy, pyrazinyloxy, and benzothiazolyloxy.

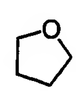
"Heterocycloalkyl" is a saturated or unsaturated ring containing carbon atoms and from 1 to about 4 (preferably 1 to 3) heteroatoms in the ring. Heterocycloalkyl rings are not aromatic. Heterocycloalkyl rings are monocyclic or bicyclic ring systems. Monocyclic heterocycloalkyl rings contain from about 3 to about 9 member atoms (carbon and heteroatoms), preferably from 5 to 7 member atoms, in the ring. Bicyclic heterocycloalkyl rings contain from 7 to 17 member atoms, preferably 7 to 12 member atoms, in the ring. Bicyclic heterocycloalkyl rings contain from about 7 to about 17 ring atoms, preferably from 7 to 12 ring atoms. Bicyclic heterocycloalkyl rings may be fused, spiro, or bridged ring systems. Preferred bicyclic heterocycloalkyl rings comprise 5-, 6- or 7-membered rings fused to 5-, 6-, or 7-membered rings. Heterocycloalkyl rings may be unsubstituted or substituted with from 1 to 4 substituents on the ring. Heterocycloalkyl may be substituted with halo, cyano, hydroxy, carboxy, keto, thioketo, amino, acylamino, acyl, amido, alkyl, heteroalkyl, haloalkyl, phenyl, alkoxy, aryloxy or any combination thereof. Preferred substituents on heterocycloalkyl include halo and haloalkyl. Preferred heterocycloalkyl rings include, but are not limited to, the following:


Oxirane


Aziridine


Oxetane


Azetidine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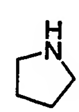
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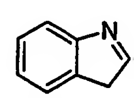
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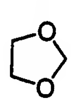
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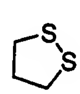
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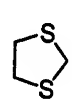
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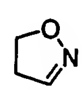
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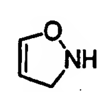
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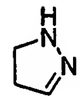
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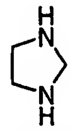
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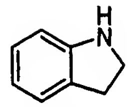
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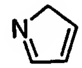
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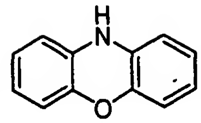
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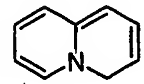
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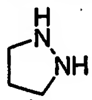
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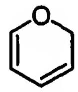
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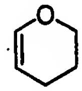
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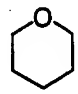
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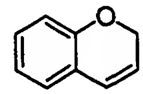
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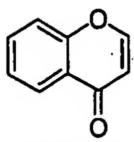
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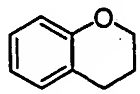
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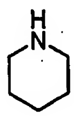
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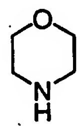
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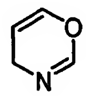
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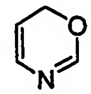
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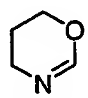
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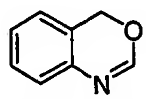
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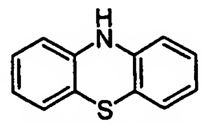
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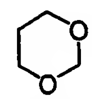
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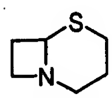
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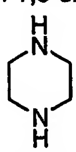
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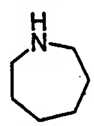
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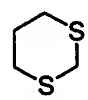
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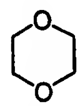
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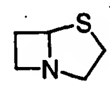
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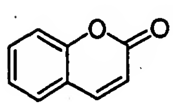
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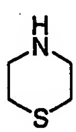
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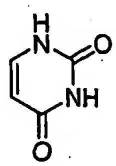
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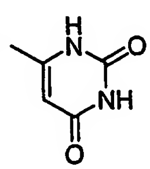
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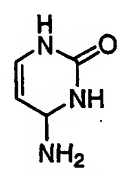
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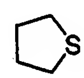
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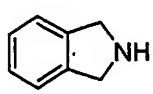
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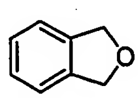
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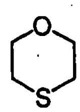
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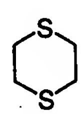
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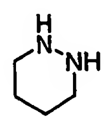
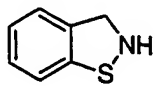
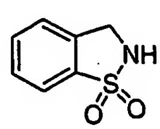

hexahydro-Pyridazine


1,2-Benzisothiazoline


Benzylsultam

"Heterocyclic ring" encompasses both heterocycloalkyl and heteroaryl moieties, as those terms are defined herein.

"Host" is a substrate capable of sustaining a microbe, preferably it is a living organism, more preferably an animal, more preferably a mammal, more preferably still a human.

The terms "optical isomer", "stereoisomer", and "diastereomer" have the standard art recognized meanings (see, e.g., Hawley's Condensed Chemical Dictionary, 11th Ed.). The illustration of specific protected forms and other derivatives of the compounds of the instant invention is not intended to be limiting. The application of other useful protecting groups, salt forms, etc. is within the ability of the skilled artisan.

The compounds of the invention may have one or more chiral centers. As a result, one may selectively prepare one optical isomer, including diastereomer and enantiomer, over another, for example by use of chiral starting materials, catalysts or solvents, one may prepare both stereoisomers or both optical isomers, including diastereomers and enantiomers at once (a racemic mixture). Since the compounds of the invention may exist as racemic mixtures, mixtures of optical isomers, including diastereomers and enantiomers, or stereoisomers, they may be separated using known methods, such as chiral resolution, chiral chromatography and the like.

In addition, it is recognized that one optical isomer, including diastereomer and enantiomer, or stereoisomer may have favorable properties over the other. Thus when disclosing and claiming the invention, when one racemic mixture is disclosed, it is clearly contemplated that both optical isomers, including diastereomers and enantiomers, or stereoisomers substantially free of the other are disclosed and claimed as well.

An "organosilicon reagent" is any silicon-containing reagent that is commonly utilized in silylation reactions, that is, reactions which substitute a hydrogen atom bound to a heteroatom (e.g., -OH, =NH, -SH, etc.) with a silyl group, usually a trialkylsilyl group, including reactions of a tautomer of a heteroatom system to form a silyl derivative (e.g., silyl emol ethers), thus forming a silicon-heteroatom bond. Many such compounds are known in the art, as described in the following articles: E. Plueddemann, "Silylating Agents", in: Kirk-Othmer, 3d ed., Vol. 20, "Encyclopedia of Chemical Technology" (1982); I. Fleming, "Organic Silicon Chemistry", in: Vol. 3, "Comprehensive Organic Chemistry" (D. Jones, editor, 1979); B. Cooper, "Silylation in Organic Synthesis", Proc. Biochem. 9 (1980); B. Cooper, "Silylation as a Protective Method in Organic Synthesis", Chem. Ind. 794 (1978); J. Rasmussen, "O-Silylated Enolates—Versatile Intermediates for Organic Synthesis" 91 Synthesis (1977). Representative organosilicon reagents

useful in the present process include, but are not limited to, chlorotrimethylsilane, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, 1,3-bis(trimethylsilyl)urea, 1,1,1,3,3,3-hexamethyldisilazane, N-methyl-N-trimethylsilyltrifluoroacetamide, 1-trimethylsilylimidazole, trimethylsilyl trifluoromethanesulfonate, tert-butyldimethylchlorosilane, 1-(tert-butyldimethylsilyl)imidazole, ethyl(trimethylsilyl)acetate, N-tert-butyldimethyl-N-methyltrifluoroacetamide, tert-butyldimethylsilyl trifluoromethanesulfonate, tert-butyldiphenylchlorosilane, tert-butyl-methoxyphenylbromosilane, dimethylphenylchlorosilane, triethylchlorosilane, triethylsilyl trifluoromethane-sulfonate, and triphenylchlorosilane. Of the various organosilicon reagents useful herein, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-trimethylsilyltrifluoroacetamide and tert-butyldiphenylchlorosilane are particularly preferred. More than one organosilicon reagent may be used in the present process.

A "pharmaceutically-acceptable salt" is a cationic salt formed at any acidic (e.g., carboxyl) group, or an anionic salt formed at any basic (e.g., amino, alkylamino, dialkylamino, morphylino, and the like) group on the compound of the invention. Since many of the compounds of the invention are zwitterionic, either salt is possible and acceptable. Many such salts are known in the art. Preferred cationic salts include the alkali metal salts (such as sodium and potassium), alkaline earth metal salts (such as magnesium and calcium) and organic salts, such as ammonio. Preferred anionic salts include halides, sulfonates, carboxylates, phosphates, and the like. Clearly contemplated in such salts are addition salts that may provide an optical center, where once there was none. For example, a chiral tartrate salt may be prepared from the compounds of the invention, and this definition includes such chiral salts. Salts contemplated are nontoxic in the amounts administered to the patient-animal, mammal or human.

The compounds made by the present process may be sufficiently basic to form acid-addition salts. The compounds are useful both in the free base form and the form of acid-addition salts, and both forms are within the purview of the invention. The acid-addition salts are in some cases a more convenient form for use. In practice, the use of the salt form inherently amounts to the use of the base form of the active. Acids used to prepare acid-addition salts include preferably those which produce, when combined with the free base, medicinally acceptable salts. These salts have anions that are relatively innocuous to the animal organism, such as a mammal, in medicinal doses of the salts so that the beneficial property inherent in the free base are not vitiated by any side effects ascribable to the acid's anions.

Examples of appropriate acid-addition salts include, but are not limited to hydrochloride, hydrobromide, hydroiodide, sulfate, hydrogensulfate, acetate, trifluoroacetate, nitrate, citrate, fumarate, formate, stearate, succinate, maleate, malonate, adipate, glutarate, lactate, propionate, butyrate, tartrate, methanesulfonate, trifluoromethanesulfonate, p-toluenesulfonate, dodecyl sulfate, cyclohexanesulfamate, and the like. However, other appropriate medicinally acceptable salts within the scope of the invention are those derived from other mineral acids and organic acids. The acid-addition salts of the basic compounds are prepared by several methods. For example, the free base can be dissolved in an aqueous alcohol solution containing the appropriate acid and the salt is isolated by evaporation of the solution. Alternatively, they may be prepared by reacting the free base with an acid in an organic solvent so that the salt separates directly. Where separation of the salt is difficult, it can be precipitated with a second organic solvent, or can be obtained by concentration of the solution.

Although medicinally acceptable salts of the basic compounds are preferred, all acid-addition salts are within the scope of the present invention. All acid-addition salts are useful as sources of the free base form, even if the particular salt per se is desired only as an intermediate product. For example, when the salt is formed only for purposes of purification or identification, or when it is used as an intermediate in preparing a medicinally acceptable salt by ion exchange procedures, these salts are clearly contemplated to be a part of this invention.

Such salts are well understood by the skilled artisan, and the skilled artisan is able to prepare any number of salts given the knowledge in the art. Furthermore, it is recognized that the skilled artisan may prefer one salt over another for reasons of solubility, stability, formulation ease and the like. Determination and optimization of such salts is within the purview of the skilled artisan's practice.

As used herein, a "quinolone derivative" includes prodrugs of a quinolone, or an active drug made from a quinolone. Preferably, such derivatives include lactams (e.g., cephems, carbacephems, penems, monolactams, etc.) covalently linked to the quinolone optionally via a spacer. Such derivatives and methods to make and use them are apparent to the skilled artisan, given the teachings of this specification.

"Spirocycle" is an alkyl or heteroalkyl diradical substituent of alkyl or heteroalkyl wherein said diradical substituent is attached geminally and wherein said diradical substituent forms a ring, said ring containing 4 to 8 member atoms (carbon or heteroatom), preferably 5 or 6 member atoms.

A "solvate" is a complex formed by the combination of a solute (e.g., a quinolone) and a solvent (e.g., water). See J. Honig et al., The Van Nostrand Chemist's Dictionary, p. 650 (1953). Pharmaceutically-acceptable solvents used according to this invention include those that do not interfere with the biological activity of the quinolone (e.g., water, ethanol, acetic acid, N,N-dimethylformamide and others known or readily determined by the skilled artisan).

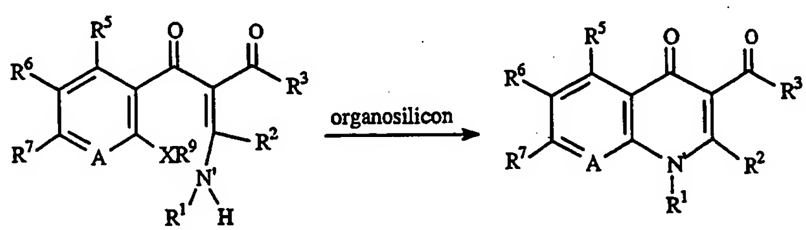
While alkyl, heteroalkyl, cycloalkyl, and heterocycloalkyl groups may be substituted with hydroxy, amino, and amido groups as stated above, the following are not envisioned in the invention:

1. Enols (OH attached to a carbon bearing a double bond).
2. Amino groups attached to a carbon bearing a double bond (except for vinylogous amides).
3. More than one hydroxy, amino, or amido attached to a single carbon (except where two nitrogen atoms are attached to a single carbon atom and all three atoms are member atoms within a heterocycloalkyl ring).
4. Hydroxy, amino, or amido attached to a carbon that also has a heteroatom attached to it.
5. Hydroxy, amino, or amido attached to a carbon that also has a halogen attached to it.

The illustration of the use of specific protected forms and other derivatives of the Formula 1 compounds in the present process are not intended to be limiting. The application of other useful protecting groups, salt forms, etc. is within the ability of the skilled artisan.

II. Preferred Compounds Made By the Subject Process:

The subject invention relates to a process comprising the following process step:



Formula (A) Formula (I)

where R^1, R^2, R^3, R^5, R^6, R^7, A, X and R^9 are as defined in the Summary of the Invention section above.

With reference to Formula (I) and Formula (A), the description above indicates that in one embodiment (defined in sub-part (A)), the nucleus of the final compounds of Formula (I) will include two fused rings as depicted. Alternatively, the nucleus of the Formula (I) compounds will, upon cyclization via the present process, include three fused rings, as defined in sub-parts (B) and (C). These alternative embodiments are depicted as Formula (B) and Formula (C), respectively, below.

In the above structures, R^5 is selected from hydrogen, alkyl, aryl, cyano, a heterocyclic ring, amino, alkylamino, arylamino, alkylacyl, arylacyl, and aryl esters and amides of carboxy. Preferred R^5 is selected from hydrogen, C_1 to about C_4 alkyl, phenyl, amino and C_1 to about C_4 mono- or dialkylamino. More preferred R^5 is selected form hydrogen, amino, methyl, ethyl, methylamino and dimethylamino. Alkyl and aryl portions of the R^5 moieties are preferably unsubstituted or substituted with fluoro.

In the above structures, R^6 is selected from hydrogen, halo, alkyl, aryl, a heterocyclic ring, amino, alkylamino, arylamino, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and alkyl and aryl esters and amides of carboxy. Preferred R^6 is selected from hydrogen, halo, nitro, C_1 to about C_4 alkylamino, C_1 to about C_4 alkoxy, and C_1 to about C_4 esters of hydroxy. More preferred R^6 is selected from hydrogen, fluoro, chloro, methyl, methylamino, dimethylamino, nitro, methoxy and acetoxy. Alkyl and aryl portions of the R^6 moieties are preferably unsubstituted or substituted with fluoro.

In the above structures, R^7 is selected from hydrogen, alkyl, aryl, a heterocyclic ring, amino, alkylamino, arylamino, halo, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and alkyl and aryl esters and amides of carboxy. Preferred R^7 is selected from hydrogen, halo, nitro, C_1 to about C_4 alkyl, unsubstituted amino, C_1 to about C_4 mono- or di-alkylamino, phenyl, naphthyl, a heterocyclic ring having one ring with 5 or 6 ring atoms or two fused rings with 8-10 ring atoms, C_1 to about C_4 alkylthio, phenylthio, phenoxy and C_1 to about C_4 esters of hydroxy. More preferred R^7 is selected from hydrogen, fluoro, chloro, bromo, nitro, unsubstituted amino, methylamino, dimethylamino and trifluoroacetoxy. Alkyl and aryl portions of the R^7 moieties are preferably unsubstituted or substituted with one or more fluoro atoms.

In the above structures, A is N or C-R^8, preferably C-R^8. R^8 is selected from hydrogen, alkyl, aryl, halo, a heterocyclic ring, amino, alkylamino, arylamino, alkoxy, nitro, cyano, aryloxy,

esters of hydroxy, alkylthio, arylthio, esters of thio, alkylsulfonyl, arylsulfonyl, alkylphosphonyl, arylphosphonyl, alkylacyl, arylacyl, and aryl esters and amides of carboxy. Preferred R^8 is selected form hydrogen, halo, about C_1-C_4 alkyl, phenyl, about C_1-C_4 alkoxy, about C_1-C_4 alkylthio, and phenoxy. More preferred R^8 is selected from hydrogen, fluoro, chloro, methoxy, di- and trifluoromethoxy, methylthio, di- and trifluoromethylthio, methyl, ethyl, cyclopropyl and phenyl.

In the above structures, R^1 is selected from a carbocyclic ring, a heterocyclic ring, lower alkyl, lower alkene, lower alkyne, and -CH(R^{10})(R^{11}) where R^{10} is selected from lower alkyl and phenyl and R^{11} is $-CH_2Y(O=)CR^{12}$ where R^{12} is selected from lower alkyl and phenyl and Y is selected from -NH-, -O- and -S-. Preferred R^1 is selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl and aryl. More preferred R^1 is selected from cyclopropyl, ethyl, 2,4-difluorophenyl, 2-methyl-1-acetoxypropane, 2-methyl-1-thioacetoxypropane. Akyl, cycloalkyl and aryl portions of the R^1 moieties are preferably unsubstituted or substituted with fluoro.

In the above structures, R^2 is selected from hydrogen, alkyl, aryl, a heterocyclic ring, alkylthio and arylthio. Preferred R^2 is selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylthio and phenyl. More preferred R^2 is hydrogen and methylthio.

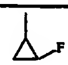
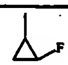
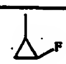
In the above structures, R^3 is selected from hydrogen, alkoxy, aryloxy, alkyl and aryl. Preferred R^3 is selected from hydrogen, about C_1-C_4 alkoxy and phenoxy. Most preferred are hydrogen, methoxy and ethoxy.

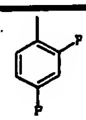
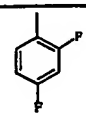
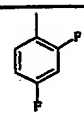
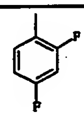
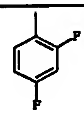
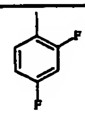
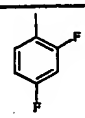
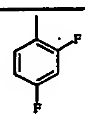
In Formula (A), X is selected from -O- and -S- and R^9 is selected from C_1-C_{10} alkyl, aryl and heteroaryl. Preferred XR^9 moieties are selected from alkoxy and alkylthio having from about 1 to about 10 carbon atoms, phenoxy and phenylthio. More preferred XR^9 moieties are selected from methoxy, ethoxy, methylthio, ethylthio, phenoxy and phenylthio, all unsubstituted.

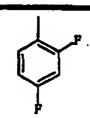
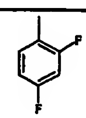
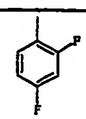
With respect to compounds defined in sub-part (A) of Formula (I), where the compounds include only two fused rings as the compound's nucleus, preferred compounds made according to the present process are those listed in Table I.

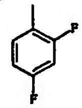
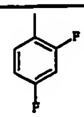
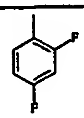
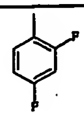
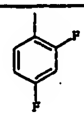
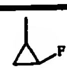
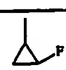
Table I

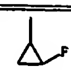
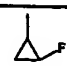
A	R^1	R^2	R^3	R^5	R^6	R^7
N		H	OMe	H	F	F
COMe		H	OMe	H	F	F

CMe		H	OMe	H	F	F
CCl		H	OMe	H	F	F
CF		H	OMe	H	F	F
CH		H	OMe	H	F	F
COCF3		H	OMe	H	F	F
COCHF2		H	OMe	H	F	F
N		H	OMe	H	F	F
COMe		H	OMe	H	F	F
CMe		H	OMe	H	F	F
CCl		H	OMe	H	F	F
CF		H	OMe	H	F	F
CH		H	OMe	H	F	F
COCF3		H	OMe	H	F	F
COCHF2		H	OMe	H	F	F
N	Et	H	OMe	H	F	F
COMe	Et	H	OMe	H	F	F
CMe	Et	H	OMe	H	F	F
CCl	Et	H	OMe	H	F	F
CF	Et	H	OMe	H	F	F
CH	Et	H	OMe	H	F	F
COCF3	Et	H	OMe	H	F	F
COCHF2	Et	H	OMe	H	F	F
N	t-But	H	OMe	H	F	F

CCl	t-But	H	OMe	H	F	F
CF	t-But	H	OMe	H	F	F
CH	t-But	H	OMe	H	F	F
N		H	OMe	H	F	F
COMe		H	OMe	H	F	F
CMe		H	OMe	H	F	F
CCl		H	OMe	H	F	F
CF		H	OMe	H	F	F
CH		H	OMe	H	F	F
COCF3		H	OMe	H	F	F
COCHF2		H	OMe	H	F	F
N		SMe	OMe	H	F	F
COMe		SMe	OMe	H	F	F
CMe		SMe	OMe	H	F	F
CCl		SMe	OMe	H	F	F

CF		SMe	OMe	H	F	F
CH		SMe	OMe	H	F	F
COCF3		SMe	OMe	H	F	F
COCHF2		SMe	OMe	H	F	F
N	Et	SMe	OEt	H	F	F
COMe	Et	SMe	OEt	H	F	F
CMe	Et	SMe	OEt	H	F	F
CCl	Et	SMe	OEt	H	F	F
CF	Et	SMe	OEt	H	F	F
CH	Et	SMe	OEt	H	F	F
COCF3	Et	SMe	OEt	H	F	F
COCHF2	Et	SMe	OEt	H	F	F
N	t-But	SMe	OEt	H	F	F
CMe	t-But	SMe	OEt	H	F	F
CCl	t-But	SMe	OEt	H	F	F
CF	t-But	SMe	OEt	H	F	F
CH	t-But	SMe	OEt	H	F	F
COCF3	t-But	SMe	OEt	H	F	F
COCHF2	t-But	SMe	OEt	H	F	F
N		SMe	OEt	H	F	F
COMe		SMe	OEt	H	F	F
CMe		SMe	OEt	H	F	F

CCl		SMe	OEt	H	F	F
CF		SMe	OEt	H	F	F
CH		SMe	OEt	H	F	F
COCF3		SMe	OEt	H	F	F
COCHF2		SMe	OEt	H	F	F
N		H	OMe	NH2	F	F
COMe		H	OMe	NH2	F	F
CMe		H	OMe	NH2	F	F
CCl		H	OMe	NH2	F	F
CF		H	OMe	NH2	F	F
CH		H	OMe	NH2	F	F
COCF3		H	OMe	NH2	F	F
COCHF2		H	OMe	NH2	F	F
N		H	OMe	NH2	F	F
COMe		H	OMe	NH2	F	F
CMe		H	OMe	NH2	F	F

CCl		H	OMe	NH2	F	F
CF		H	OMe	NH2	F	F
CH		H	OMe	NH2	F	F
COCF3		H	OMe	NH2	F	F
COCHF2		H	OMe	NH2	F	F
N	Et	H	OMe	NH2	F	F
COMe	Et	H	OMe	NH2	F	F
CMe	Et	H	OMe	NH2	F	F
CCl	Et	H	OMe	NH2	F	F
CF	Et	H	OMe	NH2	F	F
CH	Et	H	OMe	NH2	F	F
COCF3	Et	H	OMe	NH2	F	F
COCHF2	Et	H	OMe	NH2	F	F
CMe	t-But	H	OMe	NH2	F	F
CCl	t-But	H	OMe	NH2	F	F
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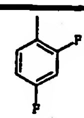
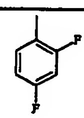
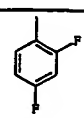
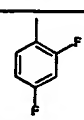
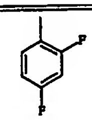
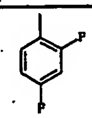
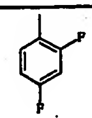
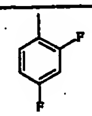
CH	t-But	H	OMe	NH2	F	F
N		H	OMe	NH2	F	F
COMe		H	OMe	NH2	F	F
CMe		H	OMe	NH2	F	F
CCl		H	OMe	NH2	F	F

CF		H	OMe	NH2	F	F
CH		H	OMe	NH2	F	F
COCF3		H	OMe	NH2	F	F
COCHF2		H	OMe	NH2	F	F
N		H	OMe	Me	F	F
COMe		H	OMe	Me	F	F
CMe		H	OMe	Me	F	F
CCl		H	OMe	Me	F	F
CF		H	OMe	Me	F	F
CH		H	OMe	Me	F	F
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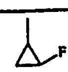
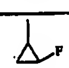
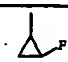
COCHF2		H	OMe	Me	F	F
N		H	OMe	Me	F	F
COMe		H	OMe	Me	F	F
CMe		H	OMe	Me	F	F
CCl		H	OMe	Me	F	F
CF		H	OMe	Me	F	F

CH		H	OMe	Me	F	F
COCF3		H	OMe	Me	F	F
COCHF2		H	OMe	Me	F	F
N	Et	H	OMe	Me	F	F
COMe	Et	H	OMe	Me	F	F
CMe	Et	H	OMe	Me	F	F
CCl	Et	H	OMe	Me	F	F
CF	Et	H	OMe	Me	F	F
CH	Et	H	OMe	Me	F	F
COCF3	Et	H	OMe	Me	F	F
COCHF2	Et	H	OMe	Me	F	F
N	t-But	H	OMe	Me	F	F
CMe	t-But	H	OMe	Me	F	F
CCl	t-But	H	OMe	Me	F	F
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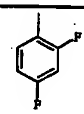
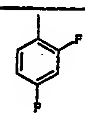
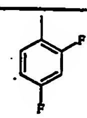
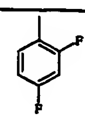
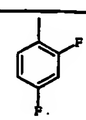
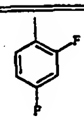
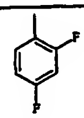
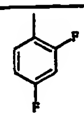
CH	t-But	H	OMe	Me	F	F
N		H	OMe	Me	F	F
COMe		H	OMe	Me	F	F
CMe		H	OMe	Me	F	F
CCl		H	OMe	Me	F	F
CF		H	OMe	Me	F	F

CH		H	OMe	Me	F	F
COCF3		H	OMe	Me	F	F
COCHF2		H	OMe	Me	F	F
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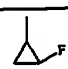
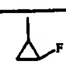
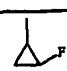
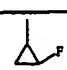
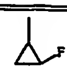
COMe		SMe	OEt	H	H	F
CMe		SMe	OEt	H	H	F
CCl		SMe	OEt	H	H	F
CF		SMe	OEt	H	H	F
CH		SMe	OEt	H	H	F
COCF3		SMe	OEt	H	H	F
COCHF2		SMe	OEt	H	H	F
N		SMe	OEt	H	H	F
COMe		SMe	OEt	H	H	F
CMe		SMe	OEt	H	H	F
CCl		SMe	OEt	H	H	F
CF		SMe	OEt	H	H	F
CH		SMe	OEt	H	H	F
COCF3		SMe	OEt	H	H	F

COCHF2		SMe	OEt	H	H	F
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COMe	Et	SMe	OEt	H	H	F
CMe	Et	SMe	OEt	H	H	F
CCl	Et	SMe	OEt	H	H	F
CF	Et	SMe	OEt	H	H	F
CH	Et	SMe	OEt	H	H	F
COCF3	Et	SMe	OEt	H	H	F
COCHF2	Et	SMe	OEt	H	H	F
N	t-But	SMe	OEt	H	H	F
CMe	t-But	SMe	OEt	H	H	F
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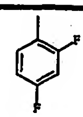
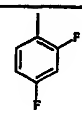
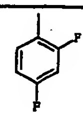
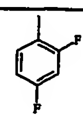
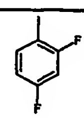
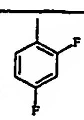
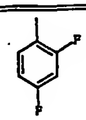
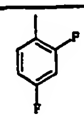
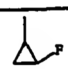
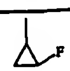
N		SMe	OEt	H	H	F
COMe		SMe	OEt	H	H	F
CMe		SMe	OEt	H	H	F
CCl		SMe	OEt	H	H	F
CF		SMe	OEt	H	H	F
CH		SMe	OEt	H	H	F

COCF3		SMe	OEt	H	H	F
COCHF2		SMe	OEt	H	H	F
N		H	OMe	NH2	H	F
COMe		H	OMe	NH2	H	F
CMe		H	OMe	NH2	H	F
CCl		H	OMe	NH2	H	F
CF		H	OMe	NH2	H	F
CH		H	OMe	NH2	H	F
COCF3		H	OMe	NH2	H	F
COCHF2		H	OMe	NH2	H	F
N		H	OMe	NH2	H	F
COMe		H	OMe	NH2	H	F
CMe		H	OMe	NH2	H	F
CCl		H	OMe	NH2	H	F
CF		H	OMe	NH2	H	F
CH		H	OMe	NH2	H	F
COCF3		H	OMe	NH2	H	F
COCHF2		H	OMe	NH2	H	F

N	Et	H	OMe	NH2	H	F
COMe	Et	H	OMe	NH2	H	F
CMe	Et	H	OMe	NH2	H	F
CCl	Et	H	OMe	NH2	H	F
CF	Et	H	OMe	NH2	H	F
CH	Et	H	OMe	NH2	H	F
COCF3	Et	H	OMe	NH2	H	F
COCHF2	Et	H	OMe	NH2	H	F
CMe	t-But	H	OMe	NH2	H	F
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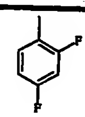
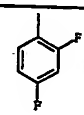
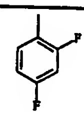
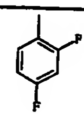
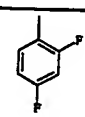
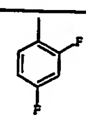
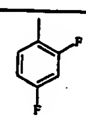
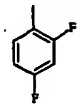
N		H	OMe	NH2	H	F
COMe		H	OMe	NH2	H	F
CMe		H	OMe	NH2	H	F
CCl		H	OMe	NH2	H	F
CF		H	OMe	NH2	H	F
CH		H	OMe	NH2	H	F
COCF3		H	OMe	NH2	H	F

COCHF2		H	OMe	NH2	H	F
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CMe		H	OMe	Me	H	F
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CF		H	OMe	Me	H	F
CH		H	OMe	Me	H	F
COCF3		H	OMe	Me	H	F
COCHF2		H	OMe	Me	H	F
N		H	OMe	Me	H	F
COMe		H	OMe	Me	H	F
CMe		H	OMe	Me	H	F
CCl		H	OMe	Me	H	F
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CH		H	OMe	Me	H	F
COCF3		H	OMe	Me	H	F
COCHF2		H	OMe	Me	H	F
N	Et	H	OMe	Me	H	F
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CCl	Et	H	OMe	Me	H	F
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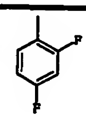
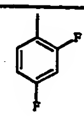
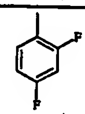
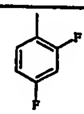
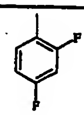
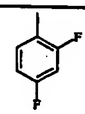
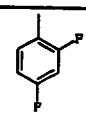
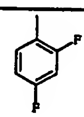
N		H	OMe	Me	H	F
COMe		H	OMe	Me	H	F
CMe		H	OMe	Me	H	F
CCl		H	OMe	Me	H	F
CF		H	OMe	Me	H	F
CH		H	OMe	Me	H	F
COCF3		H	OMe	Me	H	F
COCHF2		H	OMe	Me	H	F
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CF		H	OMe	H	Cl	F
CH		H	OMe	H	Cl	F
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COCHF2		H	OMe	H	Cl	F
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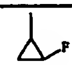
CCl		H	OMe	H	Cl	F
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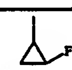
COCHF2		H	OMe	H	Cl	F
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COCHF2	Et	H	OMe	H	Cl	F
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CCl	t-But	H	OMe	H	Cl	F
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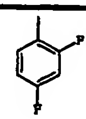
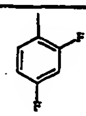
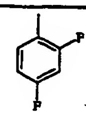
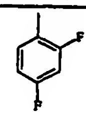
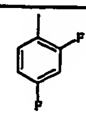
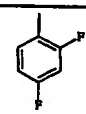
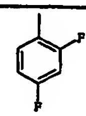
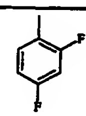
N		H	OMe	H	Cl	F
COMe		H	OMe	H	Cl	F
CMe		H	OMe	H	Cl	F
CCl		H	OMe	H	Cl	F
CF		H	OMe	H	Cl	F
CH		H	OMe	H	Cl	F
COCF3		H	OMe	H	Cl	F
COCHF2		H	OMe	H	Cl	F
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CMe		SMe	OMe	H	Cl	F

CCl		SMe	OMe	H	Cl	F
CF		SMe	OMe	H	Cl	F
CH		SMe	OMe	H	Cl	F
COCF3		SMe	OMe	H	Cl	F
COCHF2		SMe	OMe	H	Cl	F
N	Et	SMe	OMe	H	Cl	F
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CMe	Et	SMe	OMe	H	Cl	F
CCl	Et	SMe	OMe	H	Cl	F
CF	Et	SMe	OMe	H	Cl	F
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COCF3	Et	SMe	OMe	H	Cl	F
COCHF2	Et	SMe	OMe	H	Cl	F
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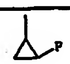
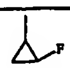
CMe		SMe	OEt	H	Cl	F
CCl		SMe	OEt	H	Cl	F
CF		SMe	OEt	H	Cl	F
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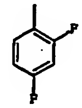
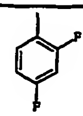
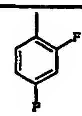
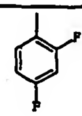
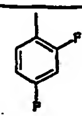
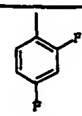
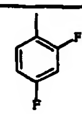
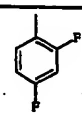
N		SMe	OEt	H	Cl	F
COMe		SMe	OEt	H	Cl	F
CMe		SMe	OEt	H	Cl	F
CCl		SMe	OEt	H	Cl	F
CF		SMe	OEt	H	Cl	F
CH		SMe	OEt	H	Cl	F
COCF3		SMe	OEt	H	Cl	F
COCHF2		SMe	OEt	H	Cl	F
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COMe		H	OMe	NH2	Cl	F
CMe		H	OMe	NH2	Cl	F
CCl		H	OMe	NH2	Cl	F
CF		H	OMe	NH2	Cl	F
CH		H	OMe	NH2	Cl	F

COCF3		H	OMe	NH2	Cl	F
COCHF2		H	OMe	NH2	Cl	F
N		H	OMe	NH2	Cl	F
COMe		H	OMe	NH2	Cl	F
CMe		H	OMe	NH2	Cl	F
CCl		H	OMe	NH2	Cl	F
CF		H	OMe	NH2	Cl	F
CH		H	OMe	NH2	Cl	F
COCF3		H	OMe	NH2	Cl	F
COCHF2		H	OMe	NH2	Cl	F
N	Et	H	OMe	NH2	Cl	F
COMe	Et	H	OMe	NH2	Cl	F
CMe	Et	H	OMe	NH2	Cl	F
CCl	Et	H	OMe	NH2	Cl	F
CF	Et	H	OMe	NH2	Cl	F
CH	Et	H	OMe	NH2	Cl	F
COCF3	Et	H	OMe	NH2	Cl	F
COCHF2	Et	H	OMe	NH2	Cl	F
N	t-But	H	OMe	NH2	Cl	F
CMe	t-But	H	OMe	NH2	Cl	F
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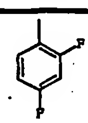
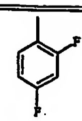
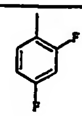
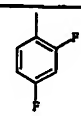
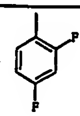
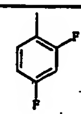
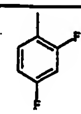
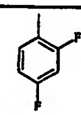
N		H	OMe	NH2	Cl	F

COMe		H	OMe	NH2	Cl	F
CMe		H	OMe	NH2	Cl	F
CCl		H	OMe	NH2	Cl	F
CF		H	OMe	NH2	Cl	F
CH		H	OMe	NH2	Cl	F
COCF3		H	OMe	NH2	Cl	F
COCHF2		H	OMe	NH2	Cl	F
N		H	OMe	Me	Cl	F
COMe		H	OMe	Me	Cl	F
CMe		H	OMe	Me	Cl	F
CCl		H	OMe	Me	Cl	F
CF		H	OMe	Me	Cl	F
CH		H	OMe	Me	Cl	F
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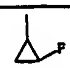
COMe		H	OMe	Me	Cl	F
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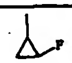
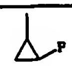
COCF3		H	OMe	Me	Cl	F
COCHF2		H	OMe	Me	Cl	F
N	Et	H	OMe	Me	Cl	F
COMe	Et	H	OMe	Me	Cl	F
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CF	Et	H	OMe	Me	Cl	F
CH	Et	H	OMe	Me	Cl	F
COCF3	Et	H	OMe	Me	Cl	F
COCHF2	Et	H	OMe	Me	Cl	F
N	t-But	H	OMe	Me	Cl	F
CMe	t-But	H	OMe	Me	Cl	F
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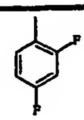
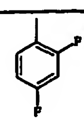
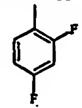
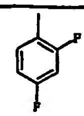
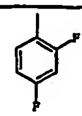
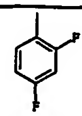
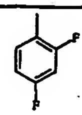
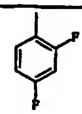
N		H	OMe	Me	Cl	F
COMe		H	OMe	Me	Cl	F

CMe		H	OMe	Me	Cl	F
CCl		H	OMe	Me	Cl	F
CF		H	OMe	Me	Cl	F
CH		H	OMe	Me	Cl	F
COCF3		H	OMe	Me	Cl	F
COCHF2		H	OMe	Me	Cl	F
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CMe		H	OMe	H	F	Br
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CH		H	OMe	H	F	Br
COCF3		H	OMe	H	F	Br
COCHF2		H	OMe	H	F	Br
N		H	OMe	H	F	Br

COMe		H	OMe	H	F	Br
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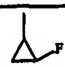
CH		H	OMe	H	F	Br
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COMe	Et	H	OMe	H	F	Br
CMe	Et	H	OMe	H	F	Br
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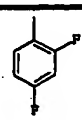
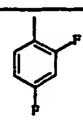
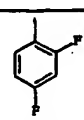
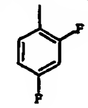
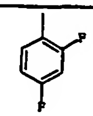
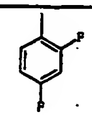
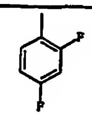
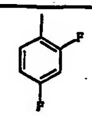
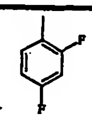
N		H	OMe	H	F	Br
COMe		H	OMe	H	F	Br
CMe		H	OMe	H	F	Br

CCl		H	OMe	H	F	Br
CF		H	OMe	H	F	Br
CH		H	OMe	H	F	Br
COCF3		H	OMe	H	F	Br
COCHF2		H	OMe	H	F	Br
N		SMe	OMe	H	F	Br
N		SMe	OEt	H	F	Br
COMe		SMe	OEt	H	F	Br
CMe		SMe	OEt	H	F	Br
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CF		SMe	OEt	H	F	Br
CH		SMe	OEt	H	F	Br
COCF3		SMe	OEt	H	F	Br
COCHF2		SMe	OEt	H	F	Br
N		SMe	OEt	H	F	Br

COMe		SMe	OEt	H	F	Br
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CCl		SMe	OEt	H	F	Br
CF		SMe	OEt	H	F	Br
CH		SMe	OEt	H	F	Br
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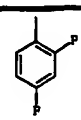
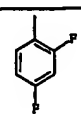
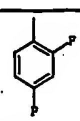
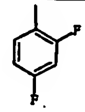
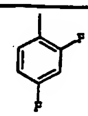
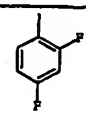
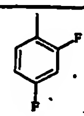
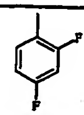
N		SMe	OEt	H	F	Br
COMe		SMe	OEt	H	F	Br
CMe		SMe	OEt	H	F	Br

CCl		SMe	OEt	H	F	Br
CF		SMe	OEt	H	F	Br
CH		SMe	OEt	H	F	Br
COCF3		SMe	OEt	H	F	Br
COCHF2		SMe	OEt	H	F	Br
N		H	OMe	NH2	F	Br
COMe		H	OMe	NH2	F	Br
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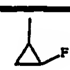
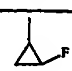
N		H	OMe	NH2	F	Br
COMe		H	OMe	NH2	F	Br
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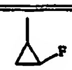
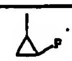
CCl		H	OMe	NH2	F	Br
CF		H	OMe	NH2	F	Br
CH		H	OMe	NH2	F	Br
COCF3		H	OMe	NH2	F	Br
COCHF2		H	OMe	NH2	F	Br
N	Et	H	OMe	NH2	F	Br
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CMe	Et	H	OMe	NH2	F	Br
CCl	Et	H	OMe	NH2	F	Br
CF	Et	H	OMe	NH2	F	Br
CH	Et	H	OMe	NH2	F	Br
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COCHF2	Et	H	OMe	NH2	F	Br
N	t-But	H	OMe	NH2	F	Br
COMe	t-But	H	OMe	NH2	F	Br
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CCl	t-But	H	OMe	NH2	F	Br
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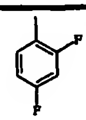
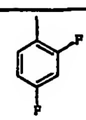
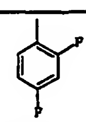
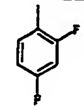
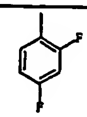
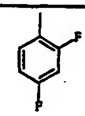
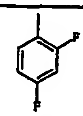
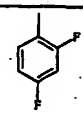
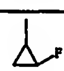
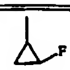
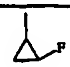
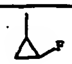
N		H	OMe	NH2	F	Br
COMe		H	OMe	NH2	F	Br
CMe		H	OMe	NH2	F	Br

CCl		H	OMe	NH2	F	Br
CF		H	OMe	NH2	F	Br
CH		H	OMe	NH2	F	Br
COCF3		H	OMe	NH2	F	Br
COCHF2		H	OMe	NH2	F	Br
N		H	OMe	Me	F	Br
COMe		H	OMe	Me	F	Br
CMe		H	OMe	Me	F	Br
CCl		H	OMe	Me	F	Br
CF		H	OMe	Me	F	Br
CH		H	OMe	Me	F	Br
COCF3		H	OMe	Me	F	Br
COCHF2		H	OMe	Me	F	Br
N		H	OMe	Me	F	Br
COMe		H	OMe	Me	F	Br
CMe		H	OMe	Me	F	Br

CCl		H	OMe	Me	F	Br
CF		H	OMe	Me	F	Br
CH		H	OMe	Me	F	Br
COCF3		H	OMe	Me	F	Br
COCHF2		H	OMe	Me	F	Br
N	Et	H	OMe	Me	F	Br
COMe	Et	H	OMe	Me	F	Br
CMe	Et	H	OMe	Me	F	Br
CCl	Et	H	OMe	Me	F	Br
CF	Et	H	OMe	Me	F	Br
CH	Et	H	OMe	Me	F	Br
COCF3	Et	H	OMe	Me	F	Br
COCHF2	Et	H	OMe	Me	F	Br
N	t-But	H	OMe	Me	F	Br
CMe	t-But	H	OMe	Me	F	Br
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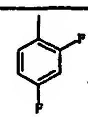
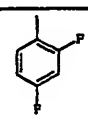
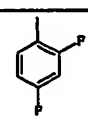
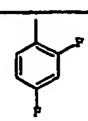
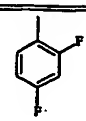
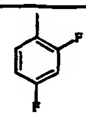
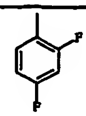
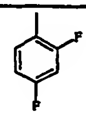
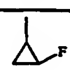
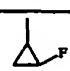
N		H	OMe	Me	F	Br
COMe		H	OMe	Me	F	Br
CMe		H	OMe	Me	F	Br
CCl		H	OMe	Me	F	Br

CF		H	OMe	Me	F	Br
CH		H	OMe	Me	F	Br
COCF3		H	OMe	Me	F	Br
COCHF2		H	OMe	Me	F	Br
N		SMe	OEt	H	H	Br
COMe		SMe	OEt	H	H	Br
CMe		SMe	OEt	H	H	Br
CCl		SMe	OEt	H	H	Br
CF		SMe	OEt	H	H	Br
CH		SMe	OEt	H	H	Br
COCF3		SMe	OEt	H	H	Br
COCHF2		SMe	OEt	H	H	Br
N		SMe	OEt	H	H	Br
COMe		SMe	OEt	H	H	Br
CMe		SMe	OEt	H	H	Br
CCl		SMe	OEt	H	H	Br
CF		SMe	OEt	H	H	Br

CH		SMe	OEt	H	H	Br
COCF3		SMe	OEt	H	H	Br
COCHF2		SMe	OEt	H	H	Br
N	Et	SMe	OEt	H	H	Br
COMe	Et	SMe	OEt	H	H	Br
CMe	Et	SMe	OEt	H	H	Br
CCl	Et	SMe	OEt	H	H	Br
CF	Et	SMe	OEt	H	H	Br
CH	Et	SMe	OEt	H	H	Br
COCF3	Et	SMe	OEt	H	H	Br
COCHF2	Et	SMe	OEt	H	H	Br
N	t-But	SMe	OEt	H	H	Br
CMe	t-But	SMe	OEt	H	H	Br
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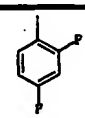
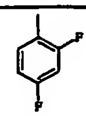
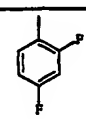
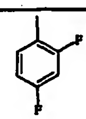
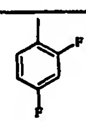
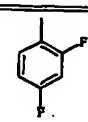
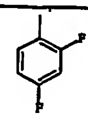
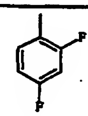
N		SMe	OEt	H	H	Br
COMe		SMe	OEt	H	H	Br
CMe		SMe	OEt	H	H	Br
CCl		SMe	OEt	H	H	Br
CF		SMe	OEt	H	H	Br

CH		SMe	OEt	H	H	Br
COCF3		SMe	OEt	H	H	Br
COCHF2		SMe	OEt	H	H	Br
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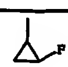
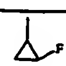
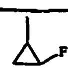
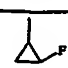
COMe		H	OMe	NH2	H	Br
CMe		H	OMe	NH2	H	Br
CCl		H	OMe	NH2	H	Br
CF		H	OMe	NH2	H	Br
CH		H	OMe	NH2	H	Br
COCF3		H	OMe	NH2	H	Br
COCHF2		H	OMe	NH2	H	Br
N		H	OMe	NH2	H	Br
COMe		H	OMe	NH2	H	Br
CMe		H	OMe	NH2	H	Br
CCl		H	OMe	NH2	H	Br
CF		H	OMe	NH2	H	Br
CH		H	OMe	NH2	H	Br
COCF3		H	OMe	NH2	H	Br

COCHF2		H	OMe	NH2	H	Br
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COMe	Et	H	OMe	NH2	H	Br
CMe	Et	H	OMe	NH2	H	Br
CCl	Et	H	OMe	NH2	H	Br
CF	Et	H	OMe	NH2	H	Br
CH	Et	H	OMe	NH2	H	Br
COCF3	Et	H	OMe	NH2	H	Br
COCHF2	Et	H	OMe	NH2	H	Br
N	t-But	H	OMe	NH2	H	Br
COMe	t-But	H	OMe	NH2	H	Br
CMe	t-But	H	OMe	NH2	H	Br
CCl	t-But	H	OMe	NH2	H	Br
CF	t-But	H	OMe	NH2	H	Br
CH	t-But	H	OMe	NH2	H	Br
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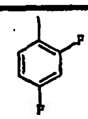
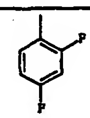
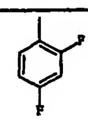
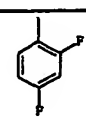
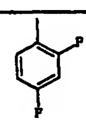
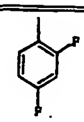
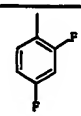
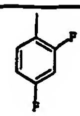
N		H	OMe	NH2	H	Br
COMe		H	OMe	NH2	H	Br
CMe		H	OMe	NH2	H	Br
CCl		H	OMe	NH2	H	Br
CF		H	OMe	NH2	H	Br

CH		H	OMe	NH2	H	Br
COCF3		H	OMe	NH2	H	Br
COCHF2		H	OMe	NH2	H	Br
N		H	OMe	Me	H	Br
COMe		H	OMe	Me	H	Br
CMe		H	OMe	Me	H	Br
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CF		H	OMe	Me	H	Br
CH		H	OMe	Me	H	Br
COCF3		H	OMe	Me	H	Br
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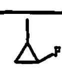
CMe		H	OMe	Me	H	Br
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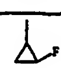
CF		H	OMe	Me	H	Br
CH		H	OMe	Me	H	Br
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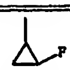
COCHF2		H	OMe	Me	H	Br
N	Et	H	OMe	Me	H	Br
COMe	Et	H	OMe	Me	H	Br
CMe	Et	H	OMe	Me	H	Br
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CH	Et	H	OMe	Me	H	Br
COCF3	Et	H	OMe	Me	H	Br
COCHF2	Et	H	OMe	Me	H	Br
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CMe	t-But	H	OMe	Me	H	Br
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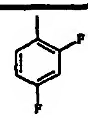
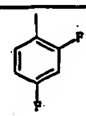
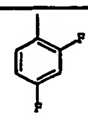
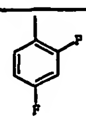
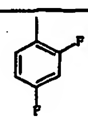
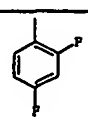
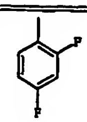
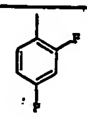
N		H	OMe	Me	H	Br
COMe		H	OMe	Me	H	Br
CMe		H	OMe	Me	H	Br
CCl		H	OMe	Me	H	Br
CF		H	OMe	Me	H	Br
CH		H	OMe	Me	H	Br

COCF3		H	OMe	Me	H	Br
COCHF2		H	OMe	Me	H	Br
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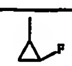
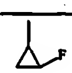
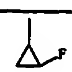
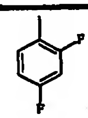
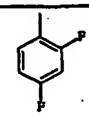
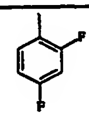
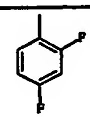
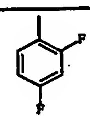
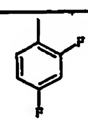
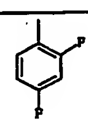
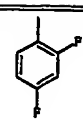
COMe		H	OMe	H	Cl	Br
CMe		H	OMe	H	Cl	Br
CCl		H	OMe	H	Cl	Br
CF		H	OMe	H	Cl	Br
CH		H	OMe	H	Cl	Br
COCF3		H	OMe	H	Cl	Br
COCHF2		H	OMe	H	Cl	Br
N		H	OMe	H	Cl	Br
COMe		H	OMe	H	Cl	Br
CMe		H	OMe	H	Cl	Br
CCl		H	OMe	H	Cl	Br
CF		H	OMe	H	Cl	Br
CH		H	OMe	H	Cl	Br
COCF3		H	OMe	H	Cl	Br
COCHF2		H	OMe	H	Cl	Br

N	Et	H	OMe	H	Cl	Br
COMe	Et	H	OMe	H	Cl	Br
CMe	Et	H	OMe	H	Cl	Br
CCl	Et	H	OMe	H	Cl	Br
CF	Et	H	OMe	H	Cl	Br
CH	Et	H	OMe	H	Cl	Br
COCF3	Et	H	OMe	H	Cl	Br
COCHF2	Et	H	OMe	H	Cl	Br
N	t-But	H	OMe	H	Cl	Br
CMe	t-But	H	OMe	H	Cl	Br
CCl	t-But	H	OMe	H	Cl	Br
CF	t-But	H	OMe	H	Cl	Br
CH	t-But	H	OMe	H	Cl	Br
N		H	OMe	H	Cl	Br
COMe		H	OMe	H	Cl	Br
CMe		H	OMe	H	Cl	Br
CCl		H	OMe	H	Cl	Br
CF		H	OMe	H	Cl	Br
CH		H	OMe	H	Cl	Br
COCF3		H	OMe	H	Cl	Br

COCHF2		H	OMe	H	Cl	Br
N		SMe	OMe	H	Cl	Br
COMe		SMe	OMe	H	Cl	Br
CMe		SMe	OMe	H	Cl	Br
CCl		SMe	OMe	H	Cl	Br
CF		SMe	OMe	H	Cl	Br
CH		SMe	OMe	H	Cl	Br
COCF3		SMe	OMe	H	Cl	Br
COCHF2		SMe	OMe	H	Cl	Br
N		SMe	OMe	H	Cl	Br
COMe		SMe	OMe	H	Cl	Br
CMe		SMe	OMe	H	Cl	Br
CCl		SMe	OMe	H	Cl	Br
CF		SMe	OMe	H	Cl	Br
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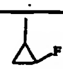
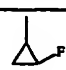
COCF3		SMe	OMe	H	Cl	Br
COCHF2		SMe	OMe	H	Cl	Br
CF		SMe	OEt	H	Cl	Br
CH		SMe	OEt	H	Cl	Br

COCF3		SMe	OEt	H	Cl	Br
COCHF2		SMe	OEt	H	Cl	Br
N	Et	SMe	OEt	H	Cl	Br
COMe	Et	SMe	OEt	H	Cl	Br
CMe	Et	SMe	OEt	H	Cl	Br
CCl	Et	SMe	OEt	H	Cl	Br
CF	Et	SMe	OEt	H	Cl	Br
CH	Et	SMe	OEt	H	Cl	Br
COCF3	Et	SMe	OEt	H	Cl	Br
COCHF2	Et	SMe	OEt	H	Cl	Br
N	t-But	SMe	OEt	H	Cl	Br
CMe	t-But	SMe	OEt	H	Cl	Br
CCl	t-But	SMe	OEt	H	Cl	Br
CMe	Et	H	OMe	H	F	NO2
CCl	Et	H	OMe	H	F	NO2
CF	Et	H	OMe	H	F	NO2
CH	Et	H	OMe	H	F	NO2
COCF3	Et	H	OMe	H	F	NO2
COCHF2	Et	H	OMe	H	F	NO2
N	t-But	H	OMe	H	F	NO2
CMe	t-But	H	OMe	H	F	NO2
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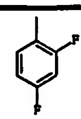
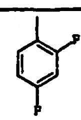
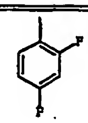
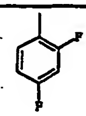
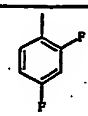
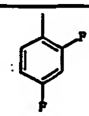
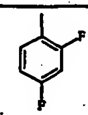
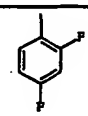
N		H	OMe	H	F	NO2
COMe		H	OMe	H	F	NO2

CMe		H	OMe	H	F	NO2
CCl		H	OMe	H	F	NO2
CF		H	OMe	H	F	NO2
CH		H	OMe	H	F	NO2
COCF3		H	OMe	H	F	NO2
COCHF2		H	OMe	H	F	NO2
N		SMe	OEt	H	F	NO2
COMe		SMe	OEt	H	F	NO2
CMe		SMe	OEt	H	F	NO2
CCl		SMe	OEt	H	F	NO2
CF		SMe	OEt	H	F	NO2
CH		SMe	OEt	H	F	NO2
COCF3		SMe	OEt	H	F	NO2
COCHF2		SMe	OEt	H	F	NO2
N		SMe	OEt	H	F	NO2

COMe		SMe	OEt	H	F	NO2
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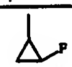
CCl		SMe	OEt	H	F	NO2
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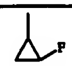
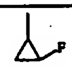
CH		SMe	OEt	H	F	NO2
COCF3		SMe	OEt	H	F	NO2
COCHF2		SMe	OEt	H	F	NO2
N	Et	SMe	OEt	H	F	NO2
COMe	Et	SMe	OEt	H	F	NO2
CMe	Et	SMe	OEt	H	F	NO2
CCl	Et	SMe	OEt	H	F	NO2
CF	Et	SMe	OEt	H	F	NO2
CH	Et	SMe	OEt	H	F	NO2
COCF3	Et	SMe	OEt	H	F	NO2
COCHF2	Et	SMe	OEt	H	F	NO2
N	t-But	SMe	OEt	H	F	NO2
CMe	t-But	SMe	OEt	H	F	NO2
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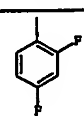
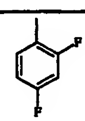
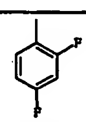
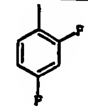
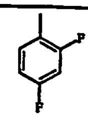
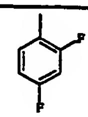
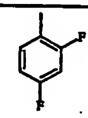
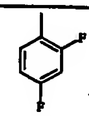
N		SMe	OEt	H	F	NO2
COMe		SMe	OEt	H	F	NO2
CMe		SMe	OEt	H	F	NO2

CCl		SMe	OEt	H	F	NO2
CF		SMe	OEt	H	F	NO2
CH		SMe	OEt	H	F	NO2
COCF3		SMe	OEt	H	F	NO2
COCHF2		SMe	OEt	H	F	NO2
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COMe		H	OMe	NH2	F	NO2
CMe		H	OMe	NH2	F	NO2
CCl		H	OMe	NH2	F	NO2
CF		H	OMe	NH2	F	NO2
CH		H	OMe	NH2	F	NO2
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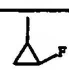
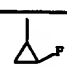
COMe		H	OMe	NH2	F	NO2
CMe		H	OMe	NH2	F	NO2

CCl		H	OMe	NH2	F	NO2
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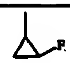
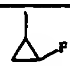
COCF3		H	OMe	NH2	F	NO2
COCHF2		H	OMe	NH2	F	NO2
N	Et	H	OMe	NH2	F	NO2
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COCF3	Et	H	OMe	NH2	F	NO2
COCHF2	Et	H	OMe	NH2	F	NO2
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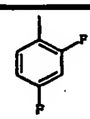
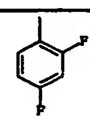
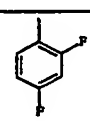
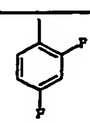
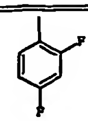
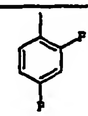
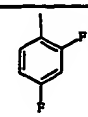
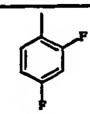
N		H	OMe	NH2	F	NO2
COMe		H	OMe	NH2	F	NO2
CMe		H	OMe	NH2	F	NO2
CCl		H	OMe	NH2	F	NO2

CF		H	OMe	NH2	F	NO2
CH		H	OMe	NH2	F	NO2
COCF3		H	OMe	NH2	F	NO2
COCHF2		H	OMe	NH2	F	NO2
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COMe		H	OMe	Me	F	NO2
CMe		H	OMe	Me	F	NO2
CCl		H	OMe	Me	F	NO2
CF		H	OMe	Me	F	NO2
CH		H	OMe	Me	F	NO2
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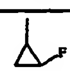
COMe		H	OMe	Me	F	NO2
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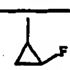
CCl		H	OMe	Me	F	NO2
CF		H	OMe	Me	F	NO2

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COCF3		H	OMe	Me	F	NO2
COCHF2		H	OMe	Me	F	NO2
N	Et	H	OMe	Me	F	NO2
COMe	Et	H	OMe	Me	F	NO2
CMe	Et	H	OMe	Me	F	NO2
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COCHF2	Et	H	OMe	Me	F	NO2
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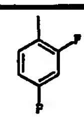
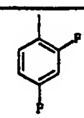
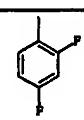
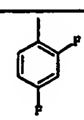
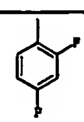
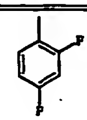
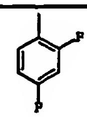
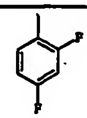
N		H	OMe	Me	F	NO2
COMe		H	OMe	Me	F	NO2
CMe		H	OMe	Me	F	NO2
CCl		H	OMe	Me	F	NO2
CF		H	OMe	Me	F	NO2

CH		H	OMe	Me	F	NO2
COCF3		H	OMe	Me	F	NO2
COCHF2		H	OMe	Me	F	NO2
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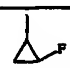
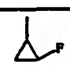
COMe		SMe	OEt	H	H	NO2
CMe		SMe	OEt	H	H	NO2
CCl		SMe	OEt	H	H	NO2
CF		SMe	OEt	H	H	NO2
CH		SMe	OEt	H	H	NO2
COCF3		SMe	OEt	H	H	NO2
COCHF2		SMe	OEt	H	H	NO2
N		SMe	OEt	H	H	NO2
COMe		SMe	OEt	H	H	NO2
CMe		SMe	OEt	H	H	NO2
CCl		SMe	OEt	H	H	NO2
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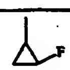
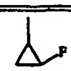
CH		SMe	OEt	H	H	NO2
COCF3		SMe	OEt	H	H	NO2

COCHF2		SMe	OEt	H	H	NO2
N	Et	SMe	OEt	H	H	NO2
COMe	Et	SMe	OEt	H	H	NO2
CMe	Et	SMe	OEt	H	H	NO2
CCl	Et	SMe	OEt	H	H	NO2
CF	Et	SMe	OEt	H	H	NO2
CH	Et	SMe	OEt	H	H	NO2
COCF3	Et	SMe	OEt	H	H	NO2
COCHF2	Et	SMe	OEt	H	H	NO2
N	t-But	SMe	OEt	H	H	NO2
CMe	t-But	SMe	OEt	H	H	NO2
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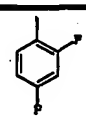
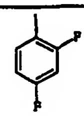
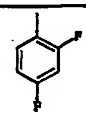
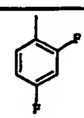
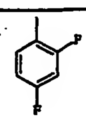
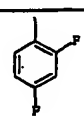
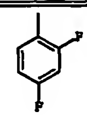
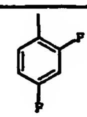
N		SMe	OEt	H	H	NO2
COMe		SMe	OEt	H	H	NO2
CMe		SMe	OEt	H	H	NO2
CCl		SMe	OEt	H	H	NO2
CF		SMe	OEt	H	H	NO2
CH		SMe	OEt	H	H	NO2

COCF3		SMe	OEt	H	H	NO2
COCHF2		SMe	OEt	H	H	NO2
N		H	OMe	NH2	H	NO2
COMe		H	OMe	NH2	H	NO2
CMe		H	OMe	NH2	H	NO2
CCl		H	OMe	NH2	H	NO2
CF		H	OMe	NH2	H	NO2
CH		H	OMe	NH2	H	NO2
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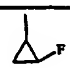
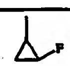
COCHF2		H	OMe	NH2	H	NO2
N		H	OMe	NH2	H	NO2
COMe		H	OMe	NH2	H	NO2
CMe		H	OMe	NH2	H	NO2
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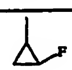
CH		H	OMe	NH2	H	NO2
COCF3		H	OMe	NH2	H	NO2
COCHF2		H	OMe	NH2	H	NO2

N	Et	H	OMe	NH2	H	NO2
COMe	Et	H	OMe	NH2	H	NO2
CMe	Et	H	OMe	NH2	H	NO2
CCl	Et	H	OMe	NH2	H	NO2
CF	Et	H	OMe	NH2	H	NO2
CH	Et	H	OMe	NH2	H	NO2
COCF3	Et	H	OMe	NH2	H	NO2
COCHF2	Et	H	OMe	NH2	H	NO2
N	t-But	H	OMe	NH2	H	NO2
CMe	t-But	H	OMe	NH2	H	NO2
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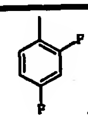
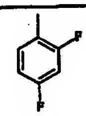
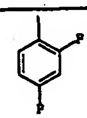
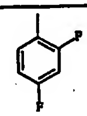
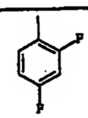
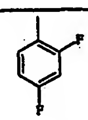
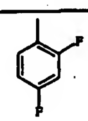
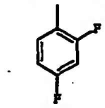
N		H	OMe	NH2	H	NO2
COMe		H	OMe	NH2	H	NO2
CMe		H	OMe	NH2	H	NO2
CCl		H	OMe	NH2	H	NO2
CF		H	OMe	NH2	H	NO2
CH		H	OMe	NH2	H	NO2
COCF3		H	OMe	NH2	H	NO2

COCHF2		H	OMe	NH2	H	NO2
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COMe		H	OMe	Me	H	NO2
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CCl		H	OMe	Me	H	NO2
CF		H	OMe	Me	H	NO2
CH		H	OMe	Me	H	NO2
COCF3		H	OMe	Me	H	NO2
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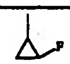
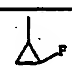
CMe		H	OMe	Me	H	NO2
CCl		H	OMe	Me	H	NO2
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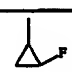
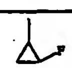
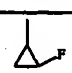
CH		H	OMe	Me	H	NO2
COCF3		H	OMe	Me	H	NO2
COCHF2		H	OMe	Me	H	NO2
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CMe	Et	H	OMe	Me	H	NO2

CCl	Et	H	OMe	Me	H	NO2
CF	Et	H	OMe	Me	H	NO2
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COCF3	Et	H	OMe	Me	H	NO2
COCHF2	Et	H	OMe	Me	H	NO2
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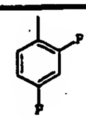
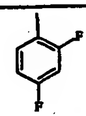
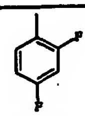
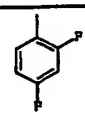
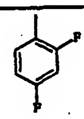
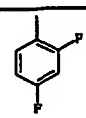
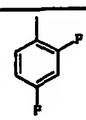
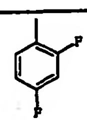
N		H	OMe	Me	H	NO2
COMe		H	OMe	Me	H	NO2
CMe		H	OMe	Me	H	NO2
CCl		H	OMe	Me	H	NO2
CF		H	OMe	Me	H	NO2
CH		H	OMe	Me	H	NO2
COCF3		H	OMe	Me	H	NO2
COCHF2		H	OMe	Me	H	NO2

N		H	OMe	H	Cl	NO2
COMe		H	OMe	H	Cl	NO2
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CF		H	OMe	H	Cl	NO2
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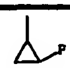
N		H	OMe	H	Cl	NO2
COMe		H	OMe	H	Cl	NO2
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CMe	Et	H	OMe	H	Cl	NO2
CCl	Et	H	OMe	H	Cl	NO2
CF	Et	H	OMe	H	Cl	NO2
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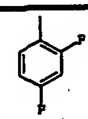
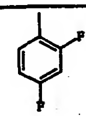
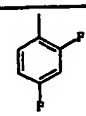
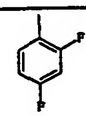
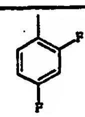
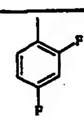
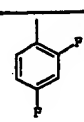
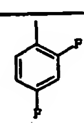
N		H	OMe	H	Cl	NO2
COMe		H	OMe	H	Cl	NO2
CMe		H	OMe	H	Cl	NO2
CCl		H	OMe	H	Cl	NO2
CF		H	OMe	H	Cl	NO2
CH		H	OMe	H	Cl	NO2
COCF3		H	OMe	H	Cl	NO2
COCHF2		H	OMe	H	Cl	NO2

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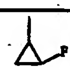
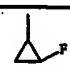
COMe		SMe	OEt	H	Cl	NO2
CMe		SMe	OEt	H	Cl	NO2
CCl		SMe	OEt	H	Cl	NO2
CF		SMe	OEt	H	Cl	NO2
CH		SMe	OEt	H	Cl	NO2
COCF3		SMe	OEt	H	Cl	NO2
COCHF2		SMe	OEt	H	Cl	NO2
N		SMe	OEt	H	Cl	NO2
COMe		SMe	OEt	H	Cl	NO2
CMe		SMe	OEt	H	Cl	NO2
CCl		SMe	OEt	H	Cl	NO2
CF		SMe	OEt	H	Cl	NO2
CH		SMe	OEt	H	Cl	NO2
COCF3		SMe	OEt	H	Cl	NO2
COCHF2		SMe	OEt	H	Cl	NO2
N	Et	SMe	OEt	H	Cl	NO2
COMe	Et	SMe	OEt	H	Cl	NO2
CMe	Et	SMe	OEt	H	Cl	NO2
CCl	Et	SMe	OEt	H	Cl	NO2
CF	Et	SMe	OEt	H	Cl	NO2
CH	Et	SMe	OEt	H	Cl	NO2

COCF3	Et	SMe	OEt	H	Cl	NO2
COCHF2	Et	SMe	OEt	H	Cl	NO2
N	t-But	SMe	OEt	H	Cl	NO2
CMe	t-But	SMe	OEt	H	Cl	NO2
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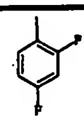
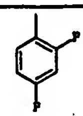
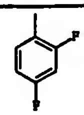
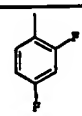
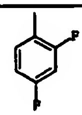
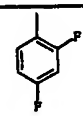
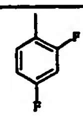
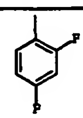
N		SMe	OEt	H	Cl	NO2
COMe		SMe	OEt	H	Cl	NO2
CMe		SMe	OEt	H	Cl	NO2
CCl		SMe	OEt	H	Cl	NO2
CF		SMe	OEt	H	Cl	NO2
CH		SMe	OEt	H	Cl	NO2
COCF3		SMe	OEt	H	Cl	NO2
COCHF2		SMe	OEt	H	Cl	NO2
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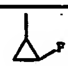
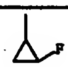
COMe		H	OMe	NH2	Cl	NO2

CMe		H	OMe	NH2	Cl	NO2
CCl		H	OMe	NH2	Cl	NO2
CF		H	OMe	NH2	Cl	NO2
CH		H	OMe	NH2	Cl	NO2
COCF3		H	OMe	NH2	Cl	NO2
COCHF2		H	OMe	NH2	Cl	NO2
N		H	OMe	NH2	Cl	NO2
COMe		H	OMe	NH2	Cl	NO2
CMe		H	OMe	NH2	Cl	NO2
CCl		H	OMe	NH2	Cl	NO2
CF		H	OMe	NH2	Cl	NO2
CH		H	OMe	NH2	Cl	NO2
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COMe	Et	H	OMe	NH2	Cl	NO2
CMe	Et	H	OMe	NH2	Cl	NO2
CCl	Et	H	OMe	NH2	Cl	NO2
CF	Et	H	OMe	NH2	Cl	NO2
CH	Et	H	OMe	NH2	Cl	NO2
COCF3	Et	H	OMe	NH2	Cl	NO2
COCHF2	Et	H	OMe	NH2	Cl	NO2
N	t-But	H	OMe	NH2	Cl	NO2

CMe	t-But	H	OMe	NH2	Cl	NO2
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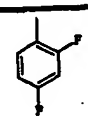
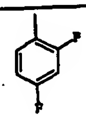
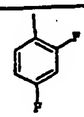
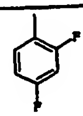
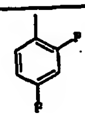
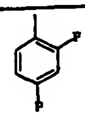
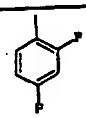
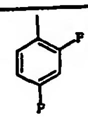
N		H	OMe	NH2	Cl	NO2
COMe		H	OMe	NH2	Cl	NO2
CMe		H	OMe	NH2	Cl	NO2
CCl		H	OMe	NH2	Cl	NO2
CF		H	OMe	NH2	Cl	NO2
CH		H	OMe	NH2	Cl	NO2
COCF3		H	OMe	NH2	Cl	NO2
COCHF2		H	OMe	NH2	Cl	NO2
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CF		H	OMe	Me	Cl	NO2
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COCF3		H	OMe	Me	Cl	NO2
COCHF2		H	OMe	Me	Cl	NO2
N		H	OMe	Me	Cl	NO2
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COMe	Et	H	OMe	Me	Cl	NO2
CMe	Et	H	OMe	Me	Cl	NO2
CCl	Et	H	OMe	Me	Cl	NO2
CF	Et	H	OMe	Me	Cl	NO2
CH	Et	H	OMe	Me	Cl	NO2
$COCF_3$	Et	H	OMe	Me	Cl	NO2
$COCHF_2$	Et	H	OMe	Me	Cl	NO2
N	t-But	H	OMe	Me	Cl	NO2
CMe	t-But	H	OMe	Me	Cl	NO2
CCl	t-But	H	OMe	Me	Cl	NO2
CF	t-But	H	OMe	Me	Cl	NO2

CH	t-But	H	OMe	Me	Cl	NO2
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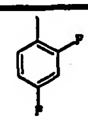
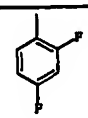
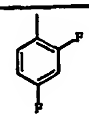
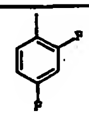
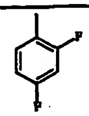
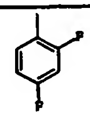
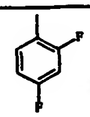
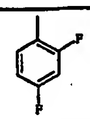
N		H	OMe	Me	Cl	NO2
COMe		H	OMe	Me	Cl	NO2
CMe		H	OMe	Me	Cl	NO2
CCl		H	OMe	Me	Cl	NO2
CF		H	OMe	Me	Cl	NO2
CH		H	OMe	Me	Cl	NO2
COCF3		H	OMe	Me	Cl	NO2
COCHF2		H	OMe	Me	Cl	NO2
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CCl		SMe	OEt	H	Me	NO2

CF		SMe	OEt	H	Me	NO2
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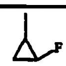
COMe		SMe	OEt	H	Me	NO2
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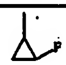
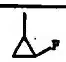
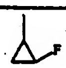
CH		SMe	OEt	H	Me	NO2
COCF3		SMe	OEt	H	Me	NO2
COCHF2		SMe	OEt	H	Me	NO2
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N	t-But	SMe	OEt	H	Me	NO2
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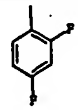
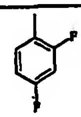
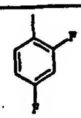
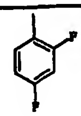
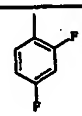
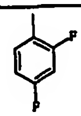
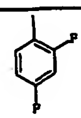
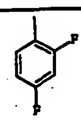
N		SMe	OEt	H	Me	NO2
COMe		SMe	OEt	H	Me	NO2
CMe		SMe	OEt	H	Me	NO2
CCl		SMe	OEt	H	Me	NO2
CF		SMe	OEt	H	Me	NO2
CH		SMe	OEt	H	Me	NO2
COCF3		SMe	OEt	H	Me	NO2
COCHF2		SMe	OEt	H	Me	NO2
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CCl		H	OMe	NH2	Me	NO2
CF		H	OMe	NH2	Me	NO2
CH		H	OMe	NH2	Me	NO2

COCF3		H	OMe	NH2	Me	NO2
COCHF2		H	OMe	NH2	Me	NO2
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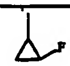
CCl		H	OMe	NH2	Me	NO2
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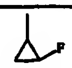
COCHF2		H	OMe	NH2	Me	NO2
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CCl	Et	H	OMe	NH2	Me	NO2
CF	Et	H	OMe	NH2	Me	NO2
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COCHF2	Et	H	OMe	NH2	Me	NO2
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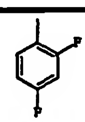
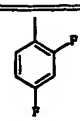
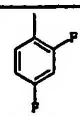
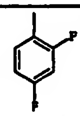
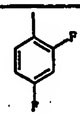
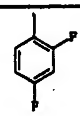
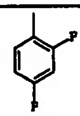
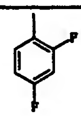
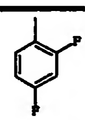
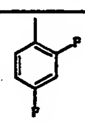
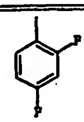
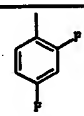
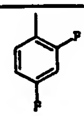
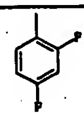
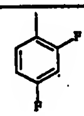
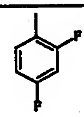
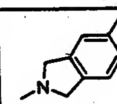
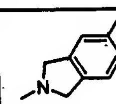
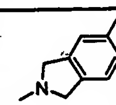
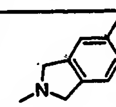
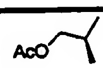
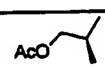
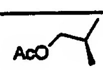
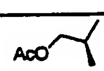
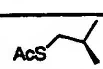
N		H	OMe	NH2	Me	NO2

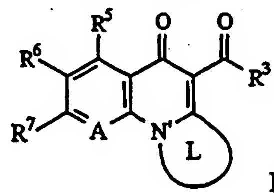
COMe		H	OMe	NH2	Me	NO2
CMe		H	OMe	NH2	Me	NO2
CCl		H	OMe	NH2	Me	NO2
CF		H	OMe	NH2	Me	NO2
CH		H	OMe	NH2	Me	NO2
COCF3		H	OMe	NH2	Me	NO2
COCHF2		H	OMe	NH2	Me	NO2
N		H	OMe	Me	Me	NO2
COMe		H	OMe	Me	Me	NO2
CMe		H	OMe	Me	Me	NO2
CCl		H	OMe	Me	Me	NO2
CF		H	OMe	Me	Me	NO2
CH		H	OMe	Me	Me	NO2
COCF3		H	OMe	Me	Me	NO2
COCHF2		H	OMe	Me	Me	NO2

N		H	OMe	Me	Me	NO2
COMe		H	OMe	Me	Me	NO2
CMe		H	OMe	Me	Me	NO2
CCl		H	OMe	Me	Me	NO2
CF		H	OMe	Me	Me	NO2
CH		H	OMe	Me	Me	NO2
COCF3		H	OMe	Me	Me	NO2
COCHF2		H	OMe	Me	Me	NO2
N	Et	H	OMe	Me	Me	NO2
COMe	Et	H	OMe	Me	Me	NO2
CMe	Et	H	OMe	Me	Me	NO2
CCl	Et	H	OMe	Me	Me	NO2
CF	Et	H	OMe	Me	Me	NO2
CH	Et	H	OMe	Me	Me	NO2
COCF3	Et	H	OMe	Me	Me	NO2
COCHF2	Et	H	OMe	Me	Me	NO2
N	t-But	H	OMe	Me	Me	NO2
CMe	t-But	H	OMe	Me	Me	NO2
CCl	t-But	H	OMe	Me	Me	NO2
CF	t-But	H	OMe	Me	Me	NO2
CH	t-But	H	OMe	Me	Me	NO2
N		H	OMe	Me	Me	NO2
COMe		H	OMe	Me	Me	NO2

CMe		H	OMe	Me	Me	NO2
CCl		H	OMe	Me	Me	NO2
CF		H	OMe	Me	Me	NO2
CH		H	OMe	Me	Me	NO2
COCF3		H	OMe	Me	Me	NO2
COCHF2		H	OMe	Me	Me	NO2
COMe		H	OEt	H	H	
COMe		H	OEt	H	F	
COMe		H	OMe	H	H	
COMe		H	OMe	H	F	
CF		H	OEt	H	F	F
CF		H	OEt	H	Cl	F
CF		H	OEt	NH_2	H	F
CF		H	OEt	Me	F	F
CF		H	OEt	H	F	F

CF		H	OEt	NH_2	F	F
CF		H	OEt	Me	Cl	F
CF		H	OEt	H	H	F

With regard to Formula (B) compounds,

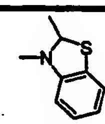
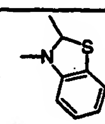
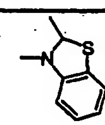
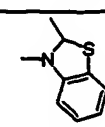
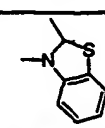


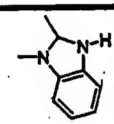
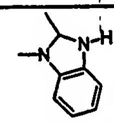
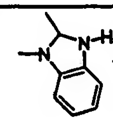
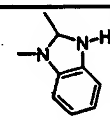
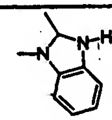
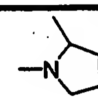
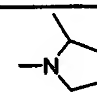
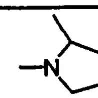
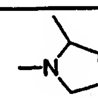
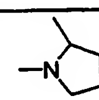
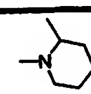
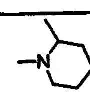
Formula (B)

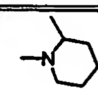
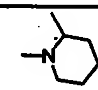
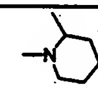
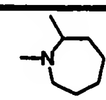
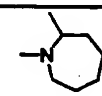
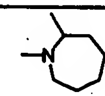
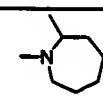
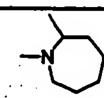
R^1 and R^2 of Formula (I) join to form ring L, which is a mono- or bicyclic heterocycle comprising N′.

Preferred compounds of Formula (B) made according to the present process are described in Table B.

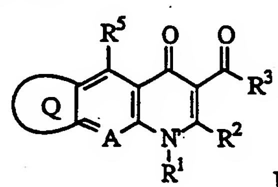
Table B

A^1	R^3	R^5	R^6	R^7	L
CH	OEt	H	F	Cl	
CH	OEt	H	Cl	F	
CF	OEt	H	F	Cl	
CH	OEt	NH_2	F	F	
CF	OEt	NH_2	F	F	

CH	OEt	H	F	F	
CH	OEt	H	Cl	F	
CF	OEt	H	F	F	
CH	OEt	NH_2	F	F	
CF	OEt	NH_2	F	F	
CH	OEt	H	F	F	
CH	OEt	H	Cl	F	
CF	OEt	H	F	F	
CH	OEt	NH_2	F	F	
CF	OEt	NH_2	F	F	
CH	OEt	H	F	F	
CH	OEt	H	Cl	F	

CF	OEt	H	F	F	
CH	OEt	NH_2	F	F	
CF	OEt	NH_2	F	F	
CH	OEt	H	F	F	
CH	OEt	H	Cl	F	
CF	OEt	H	F	F	
CH	OEt	NH_2	F	F	
CF	OEt	NH_2	F	F	

With regard to Formula (C)

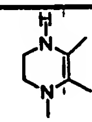
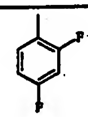
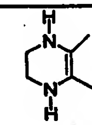
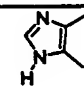
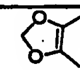
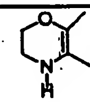
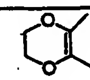
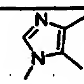


Formula (C)

R^6 and R^7 of Formula (I) join to form ring Q, which is a 5- or 6-membered carbocyclic or heterocyclic ring.

Preferred compounds of Formula (C) made according to the present process are described in Table C.

Table C

A	R^1	R^2	R^3	R^5	Q
COMe	Et	H	OEt	H	
CMe		H	OEt	Me	
CCl		H	OEt	Me	
CF		H	OEt	H	
CH	t-But	H	OEt	H	
COCF3	Et	H	OEt	H	
COCHF2		H	OEt	H	

III. <u>Process Conditions:</u>

The above subject invention process step utilizes a silylating agent that is an organosilicon reagent, which is defined above.

In the key process step, the molar ratio of the organosilicon reagent to reactant (i.e., compound of Formula (A)) is preferably from about 0.5:1 to about 12:1, more preferably from about 1:1 to about 4:1. It will be recognized that these process conditions are merely preferred ranges and is it possible to use both lower and higher molar ratios and still benefit from the inventive process.

The subject invention process step is preferably carried out in an aprotic solvent or combination of solvents. Preferred solvents in which the process step is carried out include, but are not limited to, acetonitrile, N-methylpyrrolidinone (NMP), dimethylformide, N,N-dimethylacetamide, toluene, xylene, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diglyme; more preferred solvents include acetonitrile, toluene and NMP. Mixtures of one or more solvents may be utilized.

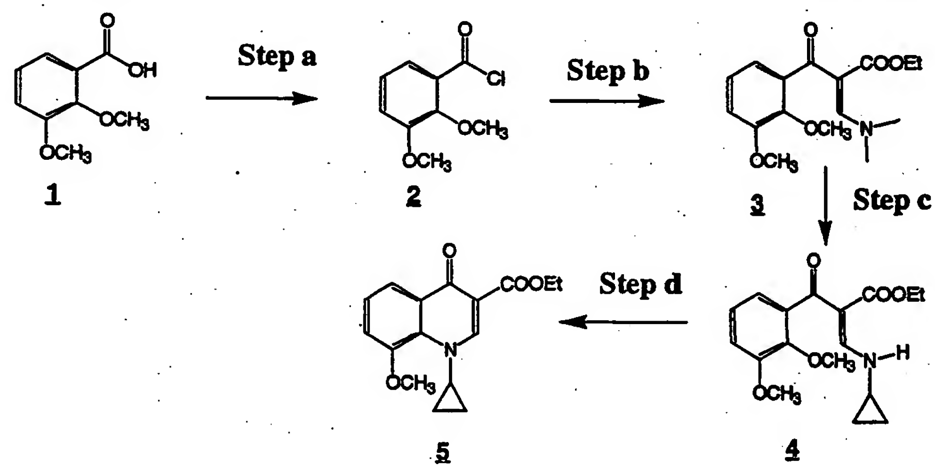
The temperature at which the subject process step is carried out is preferably from about -50°C to about 250°C, more preferably from about -10 °C to about 160°C, more preferably still from about 20°C to about 140°C. The pressure at which the subject reaction step is carried is preferably from about 0.5 atm to about 50 atm, more preferably from about 0.8 atm to about 10 atm, more preferably still from about 1 atm to about 2 atm. Also preferred is that the process step be carried out at about ambient temperature and pressure, or at about reflux temperature and ambient pressure. Again, these process conditions are merely representative and should not be interpreted as in anyway limiting the processes claimed below.

IV. Specific Synthetic Examples

The following are exemplary, but are not meant to be limiting, regarding variations of the subject invention process step.

Example 1

Preparation of Ethyl-1-cyclopropyl-1,4-dihydro-8-methoxy-4-oxo-quinoline-3-carboxylate:



Step a: To a solution of 2,3-dimethoxybenzoic acid (20 g) 1 in dichloromethane (100 ml) is added oxalyl chloride (34.83 g) followed by 2 drops of anhydrous DMF. The mixture is stirred at room temperature for 1 hr, then heated to reflux for 4h. The solvent is removed by evaporation to give 2,3-dimethoxy benzoyl chloride 2.

Step b: Product 2 is dissolved in anhydrous acetonitrile (20 mL) and is introduced to a stirred solution of triethyl amine (38.3 mL) and ethyl dimethylaminoacrylate (17.29 g) in acetonitrile (130 mL). The mixture is stirred at room temperature for 5 minutes, and then heated to reflux until the reaction goes to completion.

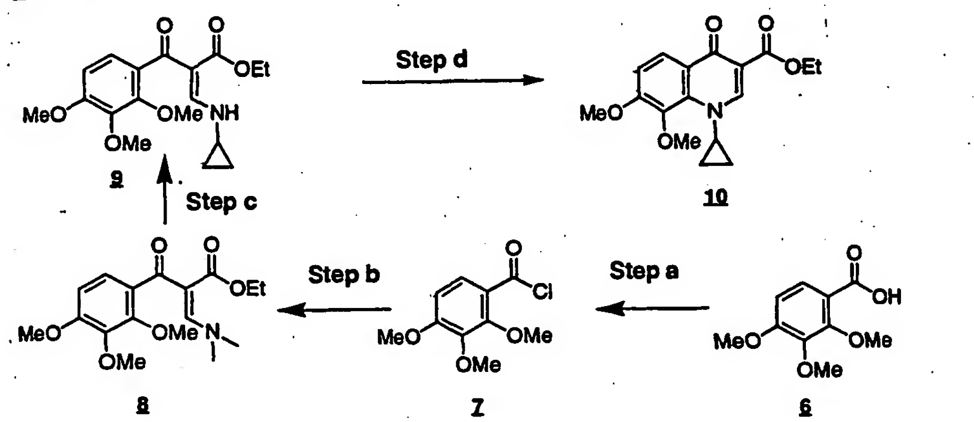
Step c: To the reaction mixture product of Step b, cyclopropylamine (19.01 mL) is added at ambient temperature and stirred until the reaction is complete. The solvent is evaporated, and

the residue is diluted with ethyl acetate, washed with water and brine, dried over anhydrous sodium sulfate and concentrated under reduced pressure to furnish product 4.

Step d: Product 4 is dissolved in anhydrous acetonitrile (150 mL). N,O-bis(trimethylsilyl)acetamide (115 g) is added. The solution is stirred at room temperature for 0.5 h and heated to reflux. Heating is continued until the reaction is complete. The reaction mixture is concentrated to an oily residue, poured into water, extracted with ethyl acetate, and the solvent removed to furnish product 5.

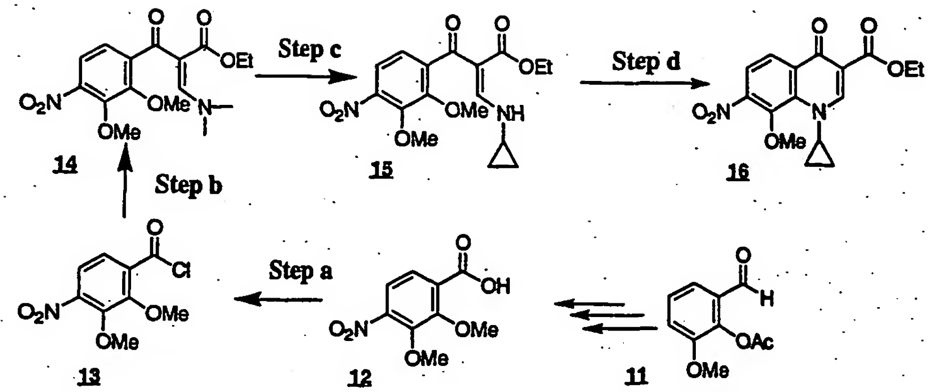
Example 2

Ethyl-1-cyclopropyl-1,4-dihydro-7,8-dimethoxy-4-oxoquinoline-3-carboxylate 10 is prepared by a process similar to that of Example 1 from commercially available 2,3,4-trimethoxy benzoic acid 6.



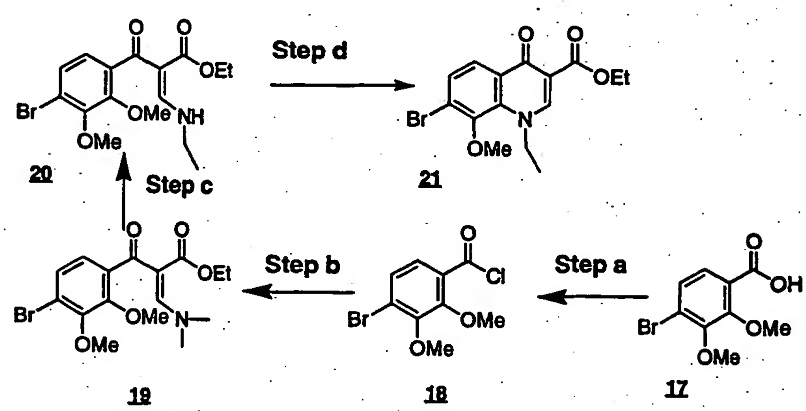
Example 3

Ethyl-1-cyclopropyl-1,4-dihydro-8-methoxy-7-nitro-4-oxoquinoline-3-carboxylate 16 is prepared by a process similar to that of Example 1 from 4-nitro-3,4-dimethoxy benzoic acid 12. The 4-nitro-3,4-dimethoxy benzoic acid is prepared from 11 according to literature procedures. (See, e.g., J. Org. Chem. 42, (6) 1068-1070 (1977) and J. Heterocyclic Chemistry 33, 1171 (1996).)



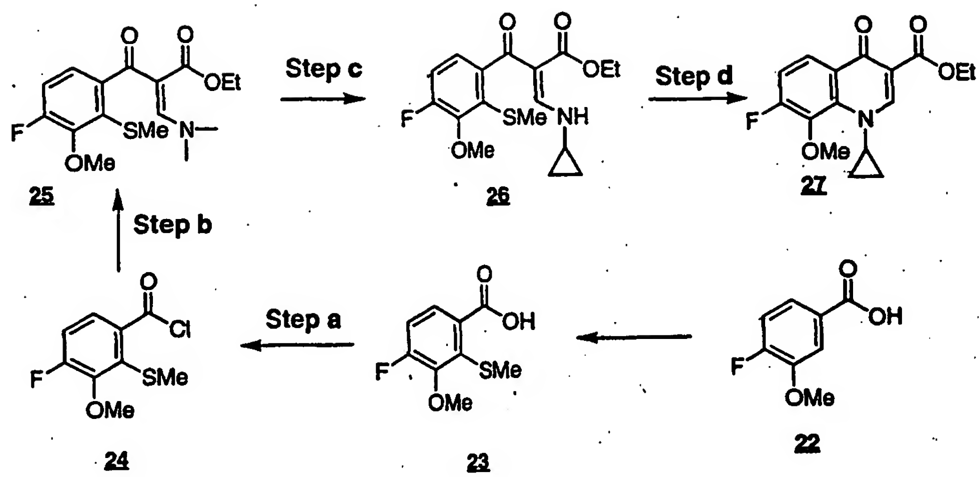
Example 4

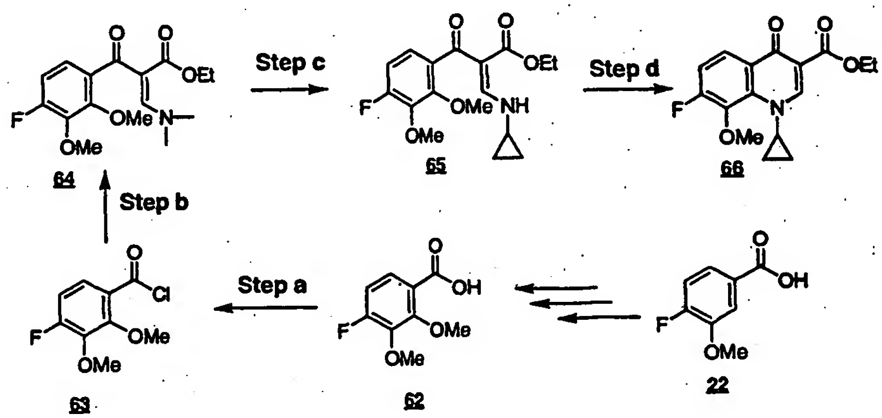
Ethyl-1-ethyl-1,4-dihydro-8-methoxy-8-bromoquinolone carboxylate 21 is prepared by a process similar to that of Example 1 from 4-bromo-3,4-dimethoxy benzoic acid 17. The 4-bromo-2,3-dimethoxy benzoic acid is prepared according to a literature method. (See e.g., J. Org. Chem. 42(6), 1068-70 (1977).)



Example 5:

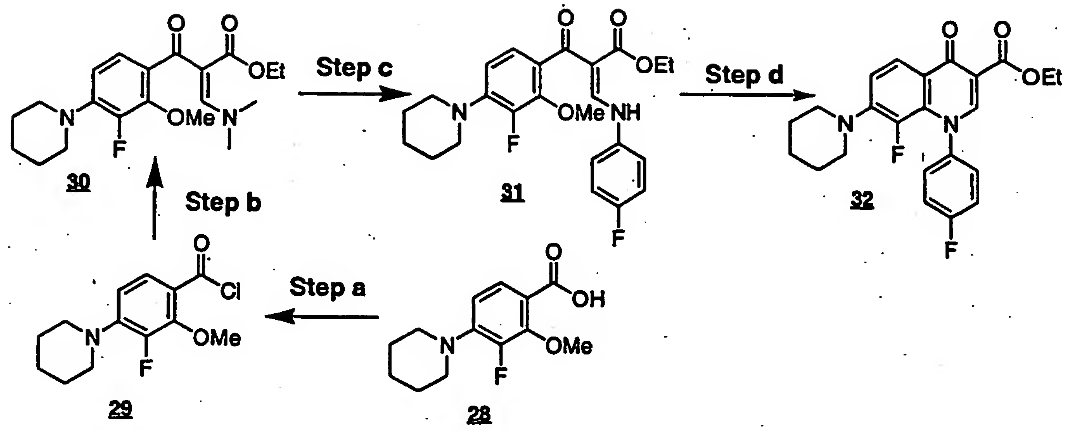
Ethyl-1-cyclopropyl-1,4-dihydro-8-methoxy-7-fluoroquinolone carboxylate 27 is prepared by a process similar to that of Example 1 from 4-fluoro-3-methoxy-2-methylthio benzoic acid 23 or 4-fluoro-2,3-dimethoxybenzoic acid 62. The starting benzoic acids are prepared from 4-fluoro-3-methoxy benzoic acid 22 by a procedure similar to that disclosed in the literature. (See, e.g., US Patent No. 5,334, 753, which is incorporated herein by reference.)





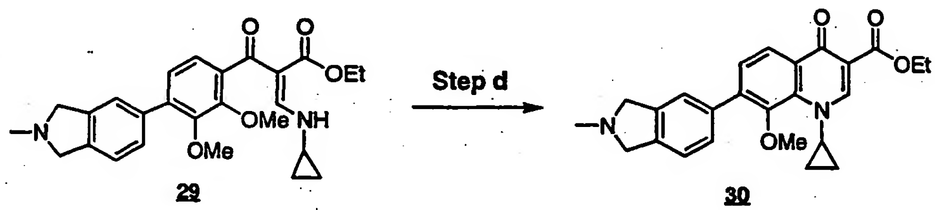
Example 6

Ethyl-1,4-dihydro-1-(4-fluorophenyl)-8-fluoro-7-piperidinyl-1,4-dihydro-4-oxo-3-quiniline carboxylic acid 32 is prepared by a process similar to that of Example 1 from 3-fluoro-2-methoxy-4-piperidinyl benzoic acid 28. The starting material 28 is prepared from 2,3,4-trifluorobenzoic acid by sequential displacement of ortho and para fluorine groups with methoxy and piperidinyl groups by a procedure similar to that reported in literature. (See e.g., Tetrahedron Letters 37 (36) 6439-6442 (1996).)



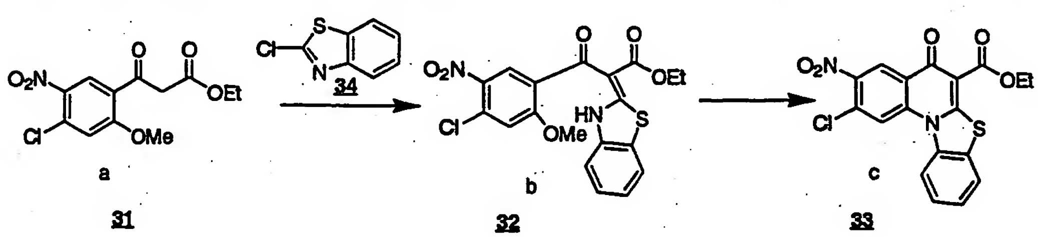
Example 7

Ethyl-1-cyclopropyl-7-isoindoline-5-yl)-8-methoxy-1,4-dihydro-4-oxoquinoline-3-carboxylate 30 is prepared by a process similar to Step d of Example 1 from the corresponding acrylate derivative 29. This acrylate derivative 29 is prepared by methods depicted in the literature. (See e.g., PCT Application No WO 97/29102.)



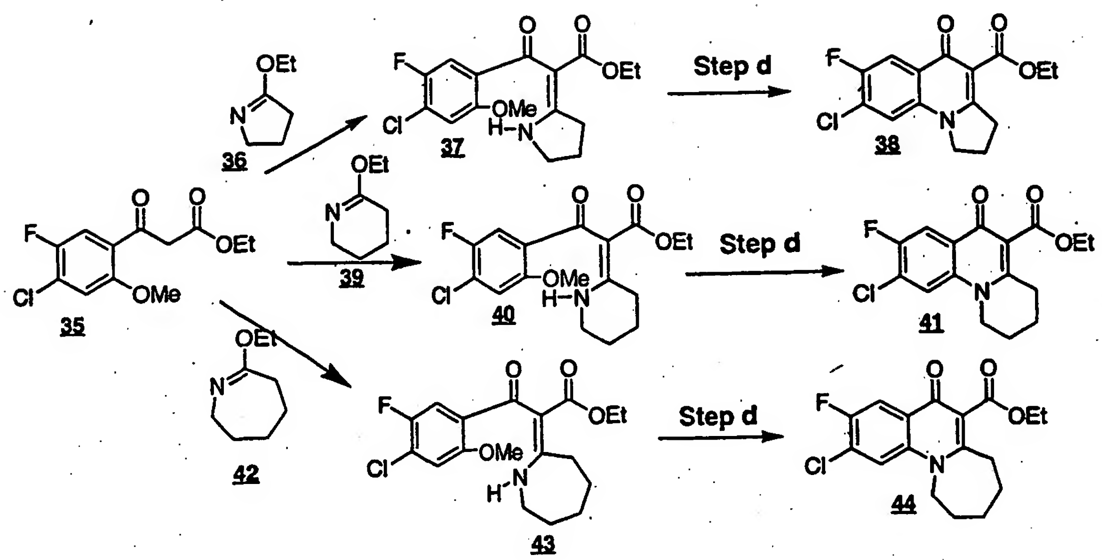
Example 8

Ethyl 2-chloro-3-nitro-5,12-dihydro-5-oxobenzothiazolo[3,2-a]quinoline-6-carboxy-late 33 is prepared by a process similar to Step d of Example 1 from its cyclization precursor 32. 32 is prepared by reacting 2-chlorobenzothiazole 34 with ethyl-2-methoxy-4-chloro-5-nitrobenzoyl acetate 31 in the presence of sodium hydride.



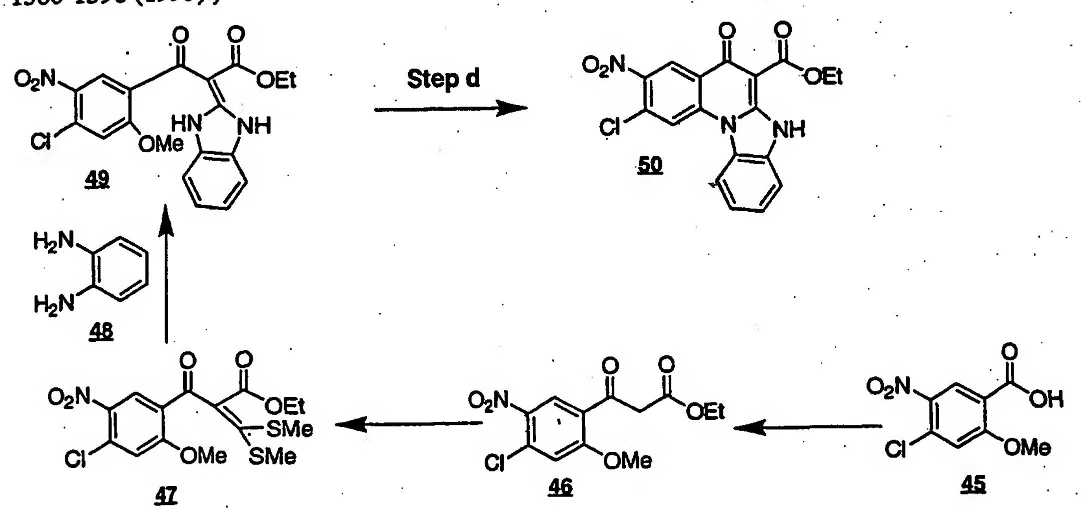
Examples 9-11

Cyclization precursors 37, 40 and 43 are prepared by condensing ethyl 2-methoxy-4-chloro-5-fluoro benzoylacetate 35 with appropriate imino ethers 36, 39 and 42, respectively. The cyclization is carried out as described in Example 1 Step d to produce 38, 41 and 44, respectively.



<u>Example 12</u>

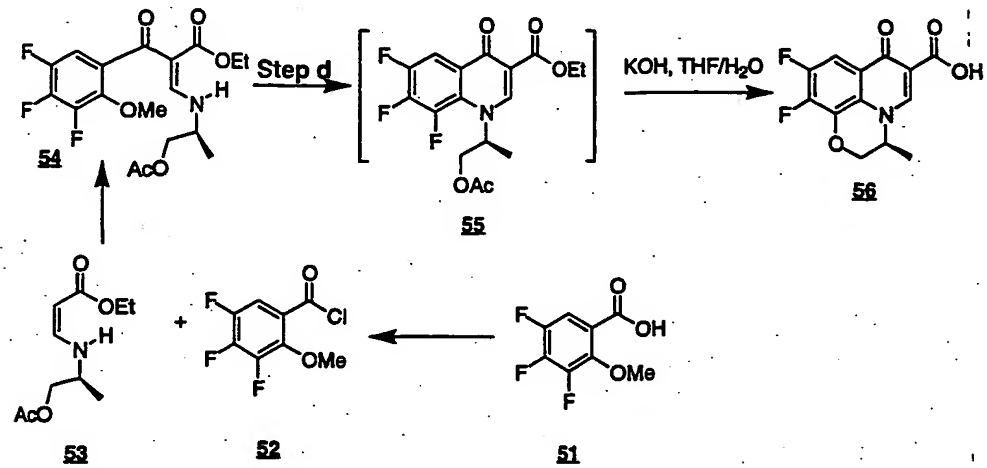
Ethyl 1,4-dihydro-4-oxo-6-nitro-7-chloro-1H-benz[d]imidazolo[2,3-a]quinoline-3-carboxylate <u>50</u> is prepared form cyclization precursor <u>49</u> as described in Step d of Example 1. The cyclization precursor <u>49</u> is prepared form 2-methoxy-4-chloro-5-nitrobenzoic acid <u>45</u> as shown below using similar procedures reported in literature. (See e.g., <u>J. Med. Chem.</u> 36 (11) 1580-1596 (1993).)



<u>Example 13</u>

(-)-9,10-Difluoro-2,3-dihydro-3(S)-methyl-7-oxo-7H-pyrido[1,2,3-de]-1,4-benzox-aine-6-carboxylic acid <u>56</u> is prepared from (+)-Ethyl 2-(2-methoxy-3,4,5-trifluorobenzoyl)-3-[(1-

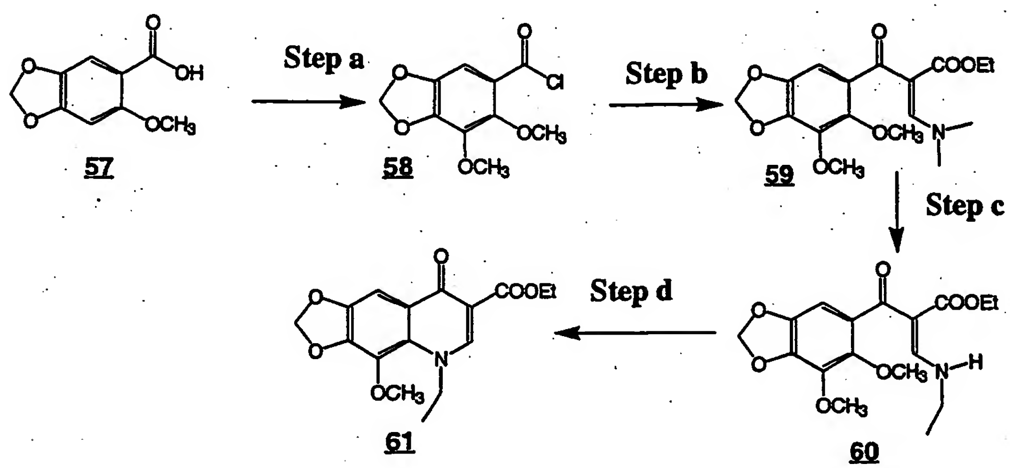
acetoxyprop-2(S)-yl)amino]acrylate 54 by first doing Step d as in Example 1, followed by refluxing the resulting reaction mixture with a 10% aq. KOH solution.



The cyclization precursor 54 is prepared from 2-methoxy-3,4,5-trifluorobenzoyl chloride 51 as shown by using literature procedures. (See E.g., in Heterocycles 45 (1), 137-145 (1997).)

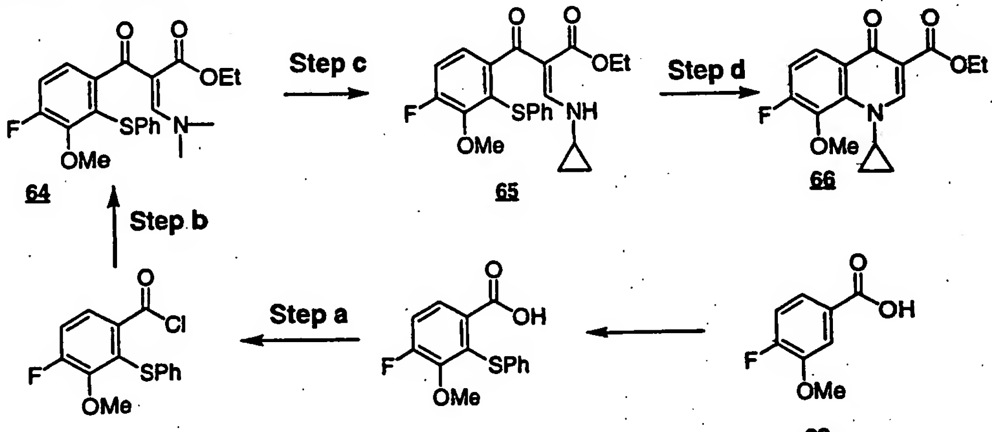
Example 14

Ethyl ester of oxolinic acid 61 is prepared by a process similar to that of Example 1 from 2-methoxy-4,5-(methylenedioxy)benzoic acid 57 as shown below. In Step c, ethylamine is used instead of cyclopropylamine.



Example 15:

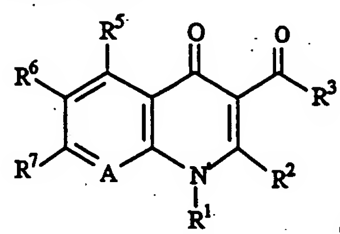
Ethyl-1-cyclopropyl-1,4-dihydro-8-methoxy-7-fluoroquinolone carboxylate 66 is prepared by a process similar to that of Example 1 from 4-fluoro-3-methoxy-2-phenylthio benzoic acid 62. The benzoic acid 62 is prepared from 4-fluoro-3-methoxy benzoic acid 22 by a procedure similar to that disclosed in literature. (See, e.g., US Patent No. 5,334, 753, which is incorporated herein by reference.)



64 65 66 63 62 22

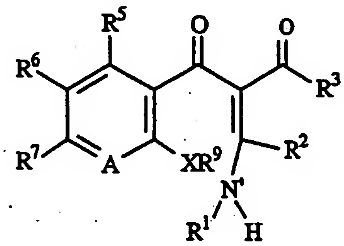
WHAT IS CLAIMED IS:

1. A process for making a compound having a structure according to Formula (I), or an optical isomer, diastereomer or enantiomer thereof, or a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof:



(I)

the process comprising reacting one or more organosilicon reagents with a compound having a structure according to Formula (A):



(A)

wherein with regard to Formula (I) and Formula (A):

(A) (1) A is N or C-R^8, where R^8 is selected from hydrogen, C_1 to about C_{15} alkyl, aryl, halo, a heterocyclic ring, amino, C_1 to about C_{15} alkylamino, arylamino, C_1 to about C_{15} alkoxy, nitro, cyano, aryloxy, esters of hydroxy, C_1 to about C_{15} alkylthio, arylthio, aryloxy, esters of thio, C_1 to about C_{15} alkylsulfonyl, arylsulfonyl, C_1 to about C_{15} alkylphosphonyl, arylphosphonyl, C_1 to about C_{15} alkylacyl, arylacyl, and aryl esters and amides of carboxy;

(2) R^7 is selected from hydrogen, C_1 to about C_{15} alkyl, aryl, a heterocyclic ring, amino, C_1 to about C_{15} alkylamino, arylamino, halo, nitro, cyano, C_1 to about C_{15} alkoxy, aryloxy, esters of hydroxy, C_1 to about C_{15} alkylthio, arylthio, esters of thio, C_1 to about C_{15} alkylsulfonyl, arylsulfonyl, C_1 to about C_{15} alkylphosphonyl, arylphosphonyl, C_1 to about C_{15} alkylacyl, arylacyl, and C_1 to about C_{15} alkyl and aryl esters and amides of carboxy;

(3) R^6 is selected from hydrogen, halo, C_1 to about C_{15} alkyl, aryl, a heterocyclic ring, amino, C_1 to about C_{15} alkylamino, arylamino, nitro, cyano, alkoxy, aryloxy, esters of hydroxy, C_1 to about C_{15} alkylthio, arylthio, esters of thio, C_1 to about C_{15} alkylsulfonyl, arylsulfonyl, C_1 to about C_{15} alkylphosphonyl, arylphosphonyl, C_1 to about C_{15} alkylacyl, arylacyl, and C_1 to about C_{15} alkyl and aryl esters and amides of carboxy;

(4) R^5 is selected from hydrogen, C_1 to about C_{15} alkyl, aryl, cyano, a heterocyclic ring, amino, C_1 to about C_{15} alkylamino, arylamino, C_1 to about C_{15} alkylacyl, arylacyl, and aryl esters and amides of carboxy;

(5) R^1 is selected from a 3 to about 17 membered carbocyclic ring, a heterocyclic ring, C_1 to about C_6 alkyl, C_1 to about C_6 alkene, C_1 to about C_6 alkyne and $-CH(R^{10})(R^{11})$ where R^{10} is selected from C_1 to about C_6 alkyl and phenyl and R^{11} is $-CH_2Y(O=)CR^{12}$ where R^{12} is selected from C_1 to about C_6 alkyl and phenyl and Y is selected from -NH-, -O- and -S-;

(6) R^2 is selected from hydrogen, C_1 to about C_{15} alkyl, aryl, a heterocyclic ring, C_1 to about C_{15} alkylthio and arylthio; and

(7) R^3 is selected from hydrogen, C_1 to about C_{15} alkoxy, aryloxy, C_1 to about C_{15} alkyl and aryl; or

(B) R^1 and R^2 can join to form a 5- or 6-membered carbocyclic or heterocyclic ring, where A, R^3, R^5, R^6, R^7 and R^8, if present, are as described in (A); or

(C) R^6 and R^7 can join to form a 5- or 6-membered carbocyclic or heterocyclic ring, where A, R^1, R^2, R^3, R^5 and R^8, if present, are as described in (A);

and wherein with regard to Formula (A):

(D) X is selected from -O- and -S- and R^9 is selected from C_1-C_{10} alkyl, aryl and heteroaryl.

2. The process of Claim 1 wherein R^9 in Formula (A) is selected from $C_1 - C_4$ alkyl and phenyl; preferably R^9 is selected from unsubstituted $C_1 - C_2$ alkyl and unsubstituted phenyl

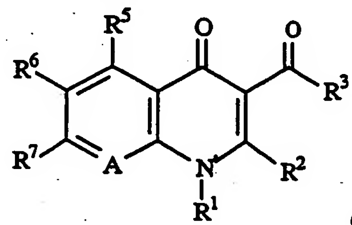
3. The process of Claim 1 wherein R^9 in Formula (A) is selected from $C_1 - C_4$ alkoxy, thio ($C_1 - C_4$) alkyl, amyloxy and thioaryl; preferably R^9 is selected from methoxy, ethoxy, propoxy, $-SCH_3$, $-SCH_2CH_3$, $-SCH_2CH_2CH_3$, phenoxy and $-S(C_6H_5)$.

4. The process of any of Claims 1 – 3 wherein none of R^1, R^2, R^6, or R^7 join together to form a ring fused to the A-containing or N′-containing rings.

5. The process of any of Claims 1 – 3 wherein R^1 and R^2 join to form a 5- or 6-membered carbocyclic or heterocyclic ring.

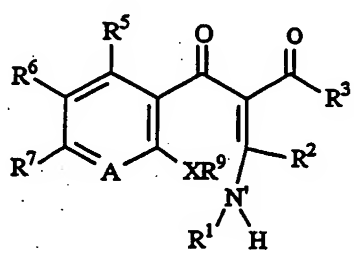
6. The process of any of Claims 1 – 3 wherein R^6 and R^7 join to form a 5- or 6-membered carbocyclic or heterocyclic ring.

7. A process for making a compound having a structure according to Formula (I), or an optical isomer, diastereomer or enantiomer thereof, or a pharmaceutically-acceptable salt, hydrate, or biohydrolyzable ester, amide or imide thereof:



(I)

the process comprising reacting one or more organosilicon reagents with a compound having a structure according to Formula (A):



(A)

wherein with regard to Formula (I) and Formula (A):

(A) (1) A is N or C-R^8, where R^8 is selected from hydrogen, halo, about C_1-C_4 alkyl, phenyl, about C_1-C_4 alkoxy, about C_1-C_4 alkylthio, and phenoxy;

(2) R^7 is selected from hydrogen, halo, nitro, C_1 to about C_4 alkyl, unsubstituted amino, C_1 to about C_4 mono- or di-alkylamino, phenyl, naphthyl, a heterocyclic ring having one ring with 5 or 6 ring atoms or two fused rings with 8-10 ring atoms, C_1 to about C_4 alkylthio, phenylthio, phenoxy and C_1 to about C_4 esters of hydroxy;

(3) R^6 is selected from hydrogen, halo, nitro, C_1 to about C_4 alkylamino, C_1 to about C_4 alkoxy, and C_1 to about C_4 esters of hydroxy;

(4) R^5 is selected from hydrogen, halo, C_1 to about C_4 alkyl, phenyl, amino and C_1 to about C_4 mono- or dialkylamino;

(5) R^1 is selected from C_1-C_4 alkyl, C_3-C_6 cycloalkyl and aryl.

(6) R^2 is selected from hydrogen, C_1-C_4 alkyl, C_1-C_4 alkylthio and phenyl; and

(7) R^3 is selected from hydrogen, about C_1-C_4 alkoxy and phenoxy;

and wherein with regard to Formula (A):

(B) X is selected from -O- and -S- and R^9 is selected from unsubstituted methyl, ethyl and phenyl.

8. The process of any of Claims 1 – 7 wherein the molar ratio of the organosilicon reagent to the compound of Formula (A) is from 0.5:1 to 12:1, more preferably from 1:1 to 4:1.

9. The process of any of Claims 1 – 8

wherein:

(A) the organosilicon reagent is selected from the group consisting of chlorotrimethylsilane, N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, 1,3-bis(trimethylsilyl)urea, 1,1,1,3,3,3-hexamethyldisilazane, N-methyl-N-trimethylsilyltrifluoroacetamide, 1-trimethylsilylimidazole, trimethylsilyl trifluoromethanesulfonate, tert-butyldimethylchlorosilane, 1-(tert-butyldimethylsilyl)imidazole, ethyl(trimethylsilyl)acetate, N-tert-butyldimethyl-N-methyltrifluoroacetamide, tert-butyldimethylsilyl trifluoromethanesulfonate, tert-butyldiphenylchlorosilane, tert-butyl-methoxyphenylbromosilane, dimethylphenylchlorosilane, triethylchlorosilane, triethylsilyl trifluoromethane-sulfonate, and triphenylchlorosilane, and mixtures thereof; preferably the organosilicon reagent is selected from N,O-bis(trimethylsilyl)acetamide, N,O-bis(trimethylsilyl)trifluoroacetamide, N-methyl-N-trimethylsilyltrifluoroacetamide and tert-butyldiphenylchlorosilane, and mixtures thereof;

(B) the organosilicon reagent and the compound of Formula (A) are reacted at a temperature of from -50°C to 250°C; preferably from -10°C to 160°C; more preferably from 20°C to 140°C; and

(C) the organosilicon reagent and the compound of Formula (A) are reacted at a pressure of from 0.5 atm to 50 atm; preferably 0.8 atm to 10 atm; more preferably from 1 atm to 2 atm.

10. The process of any of Claims 1 – 9 wherein the organosilicon reagent and the compound of Formula (A) are reacted in a solvent selected from acetonitrile, N-methylpyrrolidinone (NMP), dimethylformide, N,N-dimethylacetamide, toluene, xylene, tetrahydrofuran, dioxane, 1,2-dimethoxyethane, diglyme; more preferred solvents include acetonitrile, toluene, NMP, and mixtures of any of the foregoing.

INTERNATIONAL SEARCH REPORT

Inte d Application No
PCT/US 01/48536

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D215/56 C07D401/04 C07D513/04 C07D471/04 C07D498/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 703 231 A (GODLEWSKI JANE ELLEN ET AL) 30 December 1997 (1997-12-30) cited in the application Claim 1, examples column 24, line 21 - line 22	1-10
X	WO 96 04286 A (PROCTER & GAMBLE) 15 February 1996 (1996-02-15) Claim 1, examples	1-10
X	WO 96 04247 A (PROCTER & GAMBLE) 15 February 1996 (1996-02-15) Claim 1, examples	1-10

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
2 April 2002	09/04/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Fritz, M

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 01/48536

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			NO	970427	A	26-03-1997
			NZ	290721	A	29-03-1999
			PT	775114	T	29-09-2000
			WO	9604247	A1	15-02-1996
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